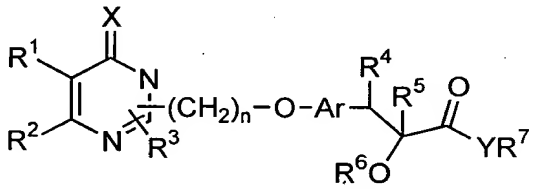
NEW HETEROCYCLIC COMPOUNDS AND THEIR USE IN MEDICINE, PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSTIONS CONTAINING THEM

Field of Invention

The present invention relates to novel antiobesity and hypocholesterolemic compounds, their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates and pharmaceutically acceptable compositions containing them. More particularly, the present invention relates to novel β-aryl-α-oxysubstituted alkylcarboxylic acids of the general formula (I), their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates and pharmaceutically acceptable compositions containing them.



(I)

The present invention also relates to a process for the preparation of the above said novel compounds, their analogs, their derivatives, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates, novel intermediates and pharmaceutical compositions containing them.

The compounds of the present invention lower total cholesterol (TC); increase high density lipoprotein (HDL) and decrease low density lipoprotein (LDL), which have beneficial effects on coronary heart disease and atherosclerosis.

The compounds of general formula (I) are useful in reducing body weight and for the treatment and/or prophylaxis of diseases such as hypertension, coronary heart disease, atherosclerosis, stroke, peripheral vascular diseases and related disorders. These compounds are useful for the treatment of familial hypercholesterolemia, hypertriglyceridemia, lowering of atherogenic lipoproteins, very low density lipoprotein (VLDL) and LDL. The compounds of the present invention can be used for the treatment of certain renal diseases including glomerulonephritis, glomerulosclerosis,

nephrotic syndrome, hypertensive nephrosclerosis, retinopathy, and nephropathy. The compounds of general formula (I) are also useful for the treatment/prophylaxis of insulin resistance (type II diabetes), leptin resistance, impaired glucose tolerance, dyslipidemia, disorders related to syndrome X such as hypertension, obesity, insulin resistance, coronary heart disease, and other cardiovascular disorders. These compounds may also be useful as aldose reductase inhibitors, for improving cognitive functions in dementia, treating diabetic complications, disorders related to endothelial cell activation, psoriasis, polycystic ovarian syndrome (PCOS), inflammatory bowel diseases, osteoporosis, myotonic dystrophy, pancreatitis, arteriosclerosis, xanthoma and for the treatment of cancer. The compounds of the present inventions are useful in the treatment and/or prophylaxis of the above said diseases in combination/ concomittant with one or more HMG CoA reductase inhibitors, and/or hypolipidemic/ hypolipoproteinemic agents such as fibric acid derivatives, nicotinic acid, cholestyramine, colestipol, or probucol.

Background of Invention

Atherosclerosis and other peripheral vascular diseases effect the quality of life of millions of people. Therefore, considerable attention has been directed towards understanding the etiology of hypercholesterolemia and hyperlipidemia and the development of effective therapeutic strategies.

Hypercholesterolemia has been defined as plasma cholesterol level that exceeds arbitrarily defined value called "normal" level. Recently, it has been accepted that "ideal" plasma levels of cholesterol are much below the "normal" level of cholesterol in the general population and the risk of coronary artery disease (CAD) increases as cholesterol level rises above the "optimum" (or "ideal") value. There is clearly a definite cause and effect-relationship between hypercholesterolemia and CAD, particularly for individuals with multiple risk factors. Most of the cholesterol is present in the esterified forms with various lipoproteins such as low density lipoprotein (LDL), intermediate density lipoprotein (IDL), high density lipoprotein (HDL) and partially as very low density lipoprotein (VLDL). Studies clearly indicate that there is an inverse correlationship between CAD and atherosclerosis with serum HDL-cholesterol concentrations. (Stampfer *et al., N. Engl. J. Med.,* **325** (1991), 373-381) and the risk of CAD increases with increasing levels of LDL and VLDL.

In CAD, generally "fatty streaks" in carotid, coronary and cerebral arteries, are found which are primarily free and esterified cholesterol. Miller *et al.*, (*Br. Med. J.*, **282** (1981), 1741-1744) have shown that increase in HDL-particles may decrease the number of sites of stenosis in coronary arteries of humans, and high level of HDL-cholesterol may protect against the progression of atherosclerosis. Picardo *et al.*, (*Arteriosclerosis* **6** (1986) 434 - 441) have shown by *in vitro* experiments that HDL is capable of removing cholesterol from cells. They suggest that HDL may deplete tissues of excess free cholesterol and transfer them to the liver (Macikinnon *et al., J. Biol. Chem.* **261** (1986), 2548-2552). Therefore, agents that increase HDL cholesterol would have therapeutic significance for the treatment of hypercholesterolemia and coronary heart diseases (CHD).

Obesity is a disease highly prevalent in affluent societies and in the developing world and is a major cause of morbidity and mortality. It is a state of excess body fat accumulation. The causes of obesity are unclear. It is believed to be of genetic origin or promoted by an interaction between the genotype and environment. Irrespective of the cause, the result is fat deposition due to imbalance between the energy intake versus energy expenditure. Dieting, exercise and appetite suppression have been a part of obesity treatment. There is a need for efficient therapy to fight this disease since it may lead to coronary heart disease, diabetes, stroke, hyperlipidemia, gout, osteo-arthritis, reduced fertility and many other psychological and social problems.

Diabetes and insulin resistance is yet another disease which severely effects the quality of life of a large population in the world. Insulin resistance is the diminished ability of insulin to exert its biological action across a broad range of concentrations. In insulin resistance, the body secretes abnormally high amounts of insulin to compensate for this defect; failing which, the plasma glucose concentration inevitably rises and develops into diabetes. Among the developed countries, diabetes mellitus is a common problem and is associated with a variety of abnormalities including obesity, hypertension, hyperlipidemia (J. Clin. Invest., (1985) 75:809-817; N. Engl. J. Med. (1987) 317:350-357; J. Clin. Endocrinol. Metab., (1988) 66 : 580 - 583; J. Clin. Invest., (1975) 68:957-969) and other renal complications (See Patent Application No. WO 95/21608). It is now increasingly being recognized that insulin resistance and relative hyperinsulinemia have a contributory role in obesity, hypertension,

atherosclerosis and type 2 diabetes mellitus. The association of insulin resistance with obesity, hypertension and angina has been described as a syndrome having insulin resistance as the central pathogenic link-Syndrome-X.

Hyperlipidemia is the primary cause of cardiovascular (CVD) and other peripheral vascular diseases. High risk of CVD is related to the higher LDL (Low Density Lipoprotein) and VLDL (Very Low Density Lipoprotein) seen in hyperlipidemia. Patients having glucose intolerance/insulin resistance in addition to hyperlipidemia have higher risk of CVD. Numerous studies in the past have shown that lowering of plasma triglycerides and total cholesterol, in particular LDL and VLDL and increasing HDL cholesterol help in preventing cardiovascular diseases.

Peroxisome proliferator activated receptors (PPAR) are members of the nuclear receptor super family. The gamma (γ) isoform of PPAR (PPARγ) has been implicated in regulating differentiation of adipocytes (Endocrinology, (1994) 135: 798-800) and energy homeostasis (Cell, (1995) 83: 803-812), whereas the alpha (α) isoform of PPAR (PPARα) mediates fatty acid oxidation (Trend. Endocrin. Metab., (1993) 4: 291-296) thereby resulting in reduction of circulating free fatty acid in plasma (Current Biol. (1995) 5: 618 –621). PPARα agonists have been found useful for the treatment of obesity (WO 97/36579). It has been recently disclosed that the hypolipidaemic effect is enhanced when the molecule has both PPARα and PPARγ agonist activity and suggested to be useful for the treatment of syndrome X (WO 97/25042). Synergism between the insulin sensitizer (PPARγ agonist) and HMG CoA reductase inhibitor has been observed which may be useful for the treatment of atherosclerosis and xanthoma. (EP 0 753 298).

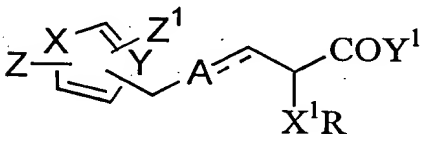
It is known that PPARγ plays an important role in adipocyte differentiation (Cell, (1996) 87, 377-389). Ligand activation of PPAR is sufficient to cause complete terminal differentiation (Cell, (1994) 79, 1147-1156) including cell cycle withdrawal. PPARγ is consistently expressed in certain cells and activation of this nuclear receptor with PPARγ agonists would stimulate the terminal differentiation of adipocyte precursors and cause morphological and molecular changes characteristics of a more differentiated, less malignant state (Molecular Cell, (1998), 465-470; Carcinogenesis, (1998), 1949-53; Proc. Natl. Acad. Sci., (1997) 94, 237-241) and inhibition of

expression of prostate cancer tissue (Cancer Research (1998), 58:3344-3352). This would be useful in the treatment of certain types of cancer, which express PPARγ and could lead to a quite nontoxic chemotherapy.

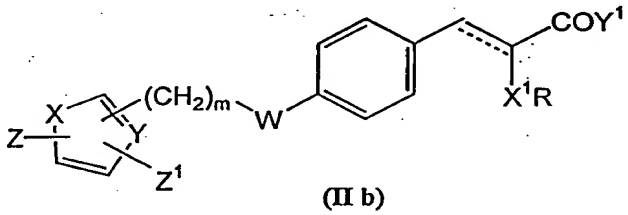
Leptin resistance is a condition wherein the target cells are unable to respond to leptin signals. This may give rise to obesity due to excess food intake and reduced energy expenditure and cause impaired glucose tolerance, type 2 diabetes, cardio-vascular diseases and such other interrelated complications. Kallen *et al* (Proc. Natl. Acad. Sci., (1996) 93, 5793-5796) have reported that insulin sensitizers which perhaps due to their PPAR agonist expression and lower plasma leptin concentrations. However, it has been recently disclosed that compounds having insulin sensitizing property also possess leptin sensitization activity. They lower the circulating plasma leptin concentrations by improving the target cell response to leptin (WO 98/02159).

A few β-aryl-α-hydroxy propionic acids, their derivatives, and their analogs have been reported to be useful in the treatment of hyperglycemia and hypercholester-olemia. Some of such compounds described in the prior art are outlined below:

i) U.S. Pat. 5,306,726 and WO 91/19702 disclose several 3-aryl-2-hydroxypropionic acid derivatives of general formula (IIa) and (IIb) as hypolipidemic and hypoglycemic agents.

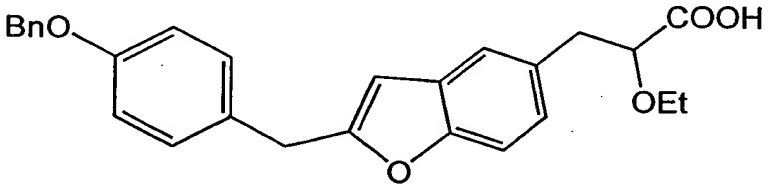


(II a)

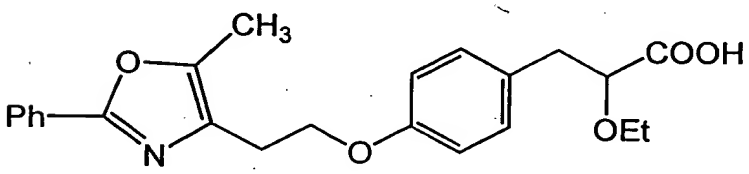


(II b)

Examples of these compounds are shown in formula (II c) and (II d)

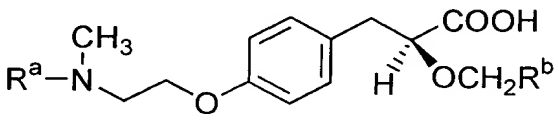


(II c)



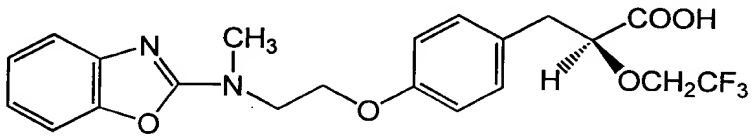
(II d)

ii) International Patent Applications, WO 95/03038 and WO 96/04260 disclose compounds of formula (II e)



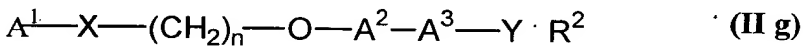
(II e)

wherein R^a represents 2-benzoxazolyl or 2-pyridyl and R^b represent CF_3, CH_2OCH_3 or CH_3. A typical example is (*S*)-3-[4-[2-[N-(2-benzoxazolyl)N-methylamino] ethoxy]phenyl]-2-(2,2,2-trifluoroethoxy)propanoic acid (II f).



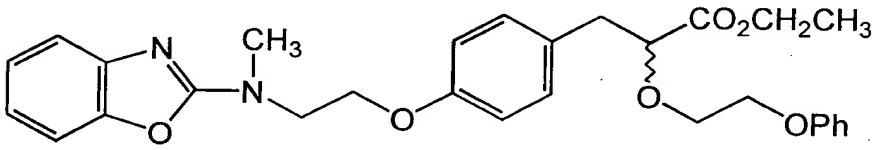
(II f)

iii) International Patent Application Nos. WO 94/13650, WO 94/01420 and WO 95/17394 disclose the compounds of general formula (II g)



(II g)

wherein A^1 represent aromatic heterocycle, A^2 represents substituted benzene ring and A^3 represents moiety of formula $(CH_2)_m$-CH-(OR^1), wherein R^1 represents alkyl groups, m is an integer of 1-5; X represents substituted or unsubstituted N; Y represents C=O or C=S, R^2 represents OR^3 where R^3 may be hydrogen, alkyl, aralkyl, or aryl group and n is an integer of 2-6. An example of these compounds is shown in formula (II h)



(II h)

Summary of the Invention

With an objective to develop novel compounds for lowering cholesterol and reducing body weight with beneficial effects in the treatment and/or prophylaxis of diseases related to increased levels of lipids, atherosclerosis, coronary artery diseases, Syndrome-X, impaired glucose tolerance, insulin resistance, insulin resistance leading to type 2 diabetes and diabetes complications thereof, for the treatment of diseases wherein insulin resistance is the pathophysiological mechanism, for the treatment and/

or prophylaxis of leptin resistance and complications thereof, hypertension, atherosclerosis and coronary artery diseases with better efficacy, potency and lower toxicity, we focussed our research to develop new compounds effective in the treatment of above mentioned diseases. Effort in this direction has led to compounds having general formula (I).

The main objective of the present invention is therefore, to provide novel β-aryl-α-oxysubstituted alkylcarboxylic acids, their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, and their pharmaceutically acceptable solvates and pharmaceutical compositions containing them, or their mixtures.

Another objective of the present invention is to provide novel β-aryl-α-oxy-substituted alkylcarboxylic acids, their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, and their pharmaceutically acceptable solvates and pharmaceutical compositions containing them or their mixtures which may have agonist activity against PPARα and/or PPARγ, and may inhibit HMG CoA reductase, in addition to agonist activity against PPARα and/or PPARγ.

Another objective of the present invention is to provide novel β-aryl-α-oxy-substituted alkylcarboxylic acids, derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, and their pharmaceutically acceptable solvates and pharmaceutical compositions containing them or their mixtures having enhanced activities, without toxic effect or with reduced toxic effect.

Yet another objective of the present invention is to produce a process for the preparation of novel β-aryl-α-oxysubstituted alkylcarboxylic acids of the formula (I) as defined above, their derivatives, their analogs, their tautomeric forms, their stereo-isomers, their polymorphs, their pharmaceutically acceptable salts and their pharma-ceutically acceptable solvates.

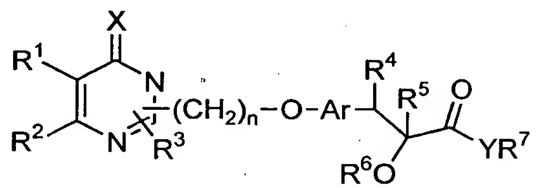
Still another objective of the present invention is to provide pharmaceutical compositions containing compounds of the general formula (I), their analogs, their derivatives, their tautomers, their stereoisomers, their polymorphs, their salts, solvates

or their mixtures in combination with suitable carriers, solvents, diluents and other media normally employed in preparing such compositions.

A further objective of the present invention is to provide novel intermediates, a process for preparation of the intermediates and a process for the preparation of novel β–aryl-α-oxysubstituted alkylcarboxylic acids of formula (I), their derivatives, their analogs, their tautomers their stereoisomers, their polymorphs, their pharmaceutically acceptable salts and their pharmaceutically acceptable solvates using the intermediates.

Detailed Description of the Invention

β-aryl α-oxysubstituted propionic acids, their derivatives and their analogs of the present invention have the general formula (I)



(I)

where X represents O or S; the groups R^1, R^2 and group R^3 when attached to the carbon atom, may be same or different and represent hydrogen, halogen, hydroxy, nitro, cyano, formyl or unsubstituted or substituted groups selected from alkyl, cyclo-alkyl, alkoxy, cycloalkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, acyloxy, hydroxyalkyl, amino, acylamino, monoalkylamino, dialkylamino, arylamino, aralkylamino, aminoalkyl, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, carboxylic acid or its derivatives, or sulfonic acid or its derivatives; or R^1, R^2 along with the adjacent atoms to which they are attached may form a 5-6 membered substituted or unsubstituted cyclic structure containing carbon atoms with one or more double bonds, which may optionally contain one or two heteroatoms selected from oxygen, nitrogen and sulfur; R^3 when attached to nitrogen atom represents hydrogen, hydroxy, formyl or unsubstituted or substituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aralkyl, heterocyclyl, heteroaryl, heteroaralkyl, acyl, acyloxy, hydroxyalkyl, amino, acylamino, mono alkylamino, dialkylamino, arylamino, aralkylamino, aminoalkyl, aryloxy, aralkoxy, heteroaryloxy, heteroaralkoxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl,

alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl groups, carboxylic acid derivatives, or sulfonic acid derivatives; the linking group represented by $-(CH_2)_n-O-$ may be attached either through nitrogen atom or through carbon atom where n is an integer ranging from $1-4$; Ar represents an unsubstituted or substituted divalent single or fused aromatic or heterocyclic group; R^4 represents hydrogen atom, hydroxy, alkoxy, halogen, lower alkyl, unsubstituted or substituted aralkyl group or forms a bond together with the adjacent group R^5; R^5 represents hydrogen, hydroxy, alkoxy, halogen, lower alkyl group, acyl, unsubstituted or substituted aralkyl or R^5 forms a bond together with R^4; R^6 may be hydrogen, or unsubstituted or substituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, alkoxyalkyl, alkoxycarbonyl, aryloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, acyl, heterocyclyl, heteroaryl, heteroaralkyl groups, with a provision that R^6 does not represent hydrogen when R^7 represents hydrogen or lower alkyl group; R^7 may be hydrogen or unsubstituted or substituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, or heteroaralkyl groups; Y represents oxygen or NR^8, where R^8 represents hydrogen or unsubstituted or substituted groups selected from, alkyl, aryl, hydroxyalkyl, aralkyl, heterocyclyl, heteroaryl, or heteroaralkyl groups; R^7 and R^8 together may form a substituted or unsubstituted 5 or 6 membered cyclic structure containing carbon atoms, which may optionally contain one or two heteroatoms selected from oxygen, sulfur or nitrogen.

Suitable groups represented by R^1, R^2 and the group R^3 when attached to carbon atom may be selected from hydrogen, halogen atom such as fluorine, chlorine, bromine, or iodine; hydroxy, cyano, nitro, formyl; substituted or unsubstituted (C_1-C_{12})alkyl group, especially, linear or branched (C_1-C_6)alkyl group, such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, t-butyl, n-pentyl, iso-pentyl, hexyl and the like; cyclo(C_3-C_6)alkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like, the cycloalkyl group may be substituted; cyclo(C_3-C_6)alkoxy group such as cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy and the like, the cycloalkoxy group may be substituted; aryl group such as phenyl or naphthyl, the aryl group may be substituted; aralkyl such as benzyl or phenethyl, $C_6H_5CH_2CH_2CH_2$, naphthylmethyl and the like, the aralkyl group may be substituted and the substituted aralkyl is a group such as $CH_3C_6H_4CH_2$, Hal-$C_6H_4CH_2$, $CH_3OC_6H_4CH_2$,

$CH_3OC_6H_4CH_2CH_2$ and the like; heteroaryl group such as pyridyl, thienyl, furyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, tetrazolyl, benzopyranyl, benzofuranyl and the like, the heteroaryl group may be substituted; heterocyclyl groups such as aziridinyl, pyrrolidinyl, morpholinyl, piperidinyl, piperazinyl and the like, the heterocyclyl group may be substituted; aralkoxy group such as benzyloxy, phenethyloxy, naphthylmethyloxy, phenylpropyloxy and the like, the aralkoxy group may be substituted; heteroaralkyl group such as furanmethyl, pyridinemethyl, oxazolemethyl, oxazolethyl and the like, the heteroaralkyl group may be substituted; aralkylamino group such as $C_6H_5CH_2NH$, $C_6H_5CH_2CH_2NH$, $C_6H_5CH_2NCH_3$ and the like, which may be substituted; alkoxycarbonyl such as methoxycarbonyl or ethoxycarbonyl, which may be substituted; aryloxycarbonyl group such as unsubstituted or substituted phenoxycarbonyl, naphthyloxycarbonyl and the like; aralkoxycarbonyl group such as benzyloxycarbonyl, phenethyloxycarbonyl, naphthylmethoxycarbonyl and the like, which may be substituted; (C_1-C_6)alkylamino group such as $NHCH_3$, NHC_2H_5, NHC_3H_7, NHC_6H_{13} and the like; which may be substituted (C_1-C_6)dialkylamino group such as $N(CH_3)_2$, $NCH_3(C_2H_5)$; and the like, which may be substituted; alkoxyalkyl group such as methoxymethyl, ethoxymethyl, methoxyethyl, ethoxyethyl and the like, which may be substituted; aryloxyalkyl group such as $C_6H_5OCH_2$, $C_6H_5OCH_2CH_2$, naphthyloxymethyl and the like, which may be substituted; aralkoxyalkyl group such as $C_6H_5CH_2OCH_2$, $C_6H_5CH_2OCH_2CH_2$ and the like, which may be substituted; heteroaryloxy and heteroaralkoxy, wherein heteroaryl and heteroaralkyl moieties are as defined earlier and may be substituted; aryloxy group such as phenoxy, naphthyloxy, the aryloxy group may be substituted; arylamino group such as HNC_6H_5, $NCH_3(C_6H_5)$, $NHC_6H_4CH_3$, NHC_6H_4-Hal and the like, which may be substituted; amino group which may be substituted; amino(C_1-C_6)alkyl which may be substituted; hydroxy(C_1-C_6)alkyl which may be substituted; (C_1-C_6)alkoxy such as methoxy, ethoxy, propyloxy, butyloxy, iso-propyloxy and the like, which may be substituted; thio(C_1-C_6)alkyl which may be substituted; (C_1-C_6)alkylthio which may be substituted; acyl group such as acetyl, propionyl or benzoyl, the acyl group may be substituted; acylamino groups such as $NHCOCH_3$, $NHCOC_2H_5$, $NHCOC_3H_7$, $NHCOC_6H_5$ which may be substituted; aralkoxycarbonylamino group such as $NHCOOCH_2C_6H_5$, $NHCOOCH_2CH_2C_6H_5$, $N(CH_3)COOCH_2C_6H_5$,

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$N(C_2H_5)COOCH_2C_6H_5$, $NHCOOCH_2C_6H_4CH_3$, $NHCOOCH_2C_6H_4OCH_3$ and the like, which may be substituted; aryloxycarbonylamino group such as $NHCOOC_6H_5$, $NCH_3COOC_6H_5$, $NC_2H_5COOC_6H_5$, $NHCOOC_6H_4CH_3$, $NHCOOC_6H_4OCH_3$ and the like which may be substituted; alkoxycarbonylamino group such as $NHCOOC_2H_5$, $NHCOOCH_3$ and the like which may be substituted; carboxylic acid or its derivatives such as amides, like $CONH_2$, CONHMe, $CONMe_2$, CONHEt, $CONEt_2$, CONHPh and the like, the carboxylic acid derivatives may be substituted; acyloxy group such as OOCMe, OOCEt, OOCPh and the like which may optionally be substituted; sulfonic acid or its derivatives such as SO_2NH_2, SO_2NHMe, SO_2NMe_2, SO_2NHCF_3 and the like, the sulfonic acid derivatives may be substituted.

When the groups represented by R^1, R^2 and the group R^3 when attached to carbon atom are substituted, the substituents may be selected from halogen, hydroxy, nitro or unsubstituted or substituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aralkyl, aralkoxyalkyl, heterocyclyl, heteroaryl, heteroaralkyl, acyl, acyloxy, hydroxyalkyl, amino, acylamino, arylamino, aminoalkyl, aryloxy, aralkoxy, alkoxycarbonyl, alkylamino, alkoxyalkyl, alkylthio, thioalkyl groups, carboxylic acid or its derivatives, or sulfonic acid or its derivatives.

It is preferred that the substituents on R^1 to R^3 represent halogen atom such as fluorine, chlorine, bromine; hydroxy group, optionally halogenated groups selected from alkyl group such as methyl, ethyl, isopropyl, n-propyl, or n-butyl; cycloalkyl group such as cyclopropyl; aryl group such as phenyl; aralkyl group such as benzyl; $(C_1\text{-}C_3)$alkoxy, benzyloxy, acyl or acyloxy groups.

Suitable cyclic structures formed by R^1 & R^2 together with the carbon atoms to which they are attached contain 5 to 6 ring atoms. The cyclic structure formed by R^1 and R^2 together with the carbon atoms to which they are attached may be a substituted or unsubstituted 5 or 6 membered cyclic structure containing carbon atoms which may optionally contain one or two heteroatoms selected from oxygen, nitrogen on sulfur. The cyclic structure may contain one or more double bonds. The cyclic structure may be optionally substituted phenyl, pyridyl, furanyl, thienyl, pyrrolyl and the like. Suitable substituents on the cyclic structure formed by R^1 & R^2 together with the adjacent carbon atoms to which they are attached include hydroxy, halogen atom such

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as chlorine, bromine and iodine; nitro, cyano, amino, formyl, (C_1-C_3)alkyl, (C_1-C_3) alkoxy, thioalkyl, and alkylthio groups.

Suitable R^3 when attached to nitrogen atom is selected from hydrogen, hydroxy, formyl; substituted or unsubstituted (C_1-C_{12})alkyl group, especially, linear or branched (C_1-C_6)alkyl group, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, t-butyl, n-pentyl, isopentyl, hexyl and the like; cyclo(C_3-C_6)alkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like, the cycloalkyl group may be substituted; cyclo(C_3-C_6)alkoxy group such as cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy and the like, the cycloalkoxy group may be substituted; aryl group such as phenyl or naphthyl, the aryl group may be substituted; aralkyl such as benzyl or phenethyl, $C_6H_5CH_2CH_2CH_2$, naphthylmethyl and the like, the aralkyl group may be substituted and the substituted aralkyl is a group such as $CH_3C_6H_4CH_2$, Hal-$C_6H_4CH_2$, $CH_3OC_6H_4CH_2$, $CH_3OC_6H_4CH_2CH_2$ and the like; heteroaryl group such as pyridyl, thienyl, furyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, tetrazolyl, benzopyranyl, benzofuranyl and the like, the heteroaryl group may be substituted; heterocyclyl groups such as aziridinyl, pyrrolidinyl, morpholinyl, piperidinyl, piperazinyl and the like, the heterocyclyl group may be substituted; aralkoxy group such as benzyloxy, phenethyloxy, naphthyl-methyloxy, phenylpropyloxy and the like, the aralkoxy group may be substituted; heteroaralkyl group such as furanmethyl, pyridinemethyl, oxazolemethyl, oxazolethyl and the like, the heteroaralkyl group may be substituted; aralkylamino group such as $C_6H_5CH_2NH$, $C_6H_5CH_2CH_2NH$, $C_6H_5CH_2NCH_3$ and the like, which may be substituted; alkoxycarbonyl such as methoxycarbonyl or ethoxycarbonyl which may be substituted; aryloxycarbonyl group such as unsubstituted or substituted phenoxy-carbonyl, naphthyloxycarbonyl and the like; aralkoxycarbonyl group such as benzyloxycarbonyl, phenethyloxycarbonyl, naphthylmethoxycarbonyl and the like, which may be substituted; (C_1-C_6)alkylamino group such as $NHCH_3$, $N(CH_3)_2$, $NCH_3(C_2H_5)$, NHC_2H_5, NHC_3H_7, NHC_6H_{13} and the like, which may be substituted; (C_1-C_6)dialkylamino group $N(CH_3)_2$, NCH_3 (C_2H_5) and the like, which may be substituted; alkoxyalkyl group such as methoxymethyl, ethoxymethyl, methoxyethyl, ethoxyethyl and the like, which may be substituted; aryloxyalkyl group such as $C_6H_5OCH_2$, $C_6H_5OCH_2CH_2$, naphthyloxymethyl and the like, which may be

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substituted; aralkoxyalkyl group such as $C_6H_5CH_2OCH_2$, $C_6H_5CH_2OCH_2CH_2$ and the like, which may be substituted; heteroaryloxy and heteroaralkoxy, wherein the heteroaryl and the heteroaralkyl moieties are as defined earlier and may be substituted; aryloxy group such as phenoxy, naphthyloxy, and the like the aryloxy group may be substituted; arylamino group such as HNC_6H_5, $NCH_3(C_6H_5)$, $NHC_6H_4CH_3$, NHC_6H_4-Hal and the like, which may be substituted; amino group which may be substituted; amino(C_1-C_6)alkyl which may be substituted; hydroxy(C_1-C_6)alkyl which may be substituted; (C_1-C_6)alkoxy such as methoxy, ethoxy, propyloxy, butyloxy, iso-propyloxy and the like which may be substituted; thio(C_1-C_6)alkyl which may be substituted; (C_1-C_6)alkylthio which may be substituted; acyl group such as acetyl, propionyl or benzoyl and the like, the acyl group may be substituted; acylamino groups such as $NHCOCH_3$, $NHCOC_2H_5$, $NHCOC_3H_7$, $NHCOC_6H_5$ which may be substituted; carboxylic acid derivatives such as amides, like $CONH_2$, CONHMe, $CONMe_2$, CONHEt, $CONEt_2$, CONHPh and the like, the carboxylic acid derivatives may be substituted; acyloxy group such as OOCMe, OOCEt, OOCPh and the like which may be substituted; sulfonic acid derivatives such as SO_2NH_2, SO_2NHMe, SO_2NMe_2, SO_2NHCF_3 and the like, the sulfonic acid derivatives may be substituted.

When the groups represented by R^3 attached to nitrogen are substituted, preferred substituents may be selected from halogen such as fluorine, chlorine; hydroxy, acyl, acyloxy, and amino groups.

n is an integer ranging from 1-4. It is preferred that n be 1 or 2.

Suitable groups represented by Ar include substituted or unsubstituted groups selected from divalent phenylene, naphthylene, pyridyl, quinolinyl, benzofuryl, dihydrobenzofuryl, benzopyranyl, indolyl, indolinyl, azaindolyl, azaindolinyl, pyrazolyl, benzothiazolyl, benzoxazolyl and the like. The substituents on the group represented by Ar may be selected from substituted or unsubstituted linear or branched (C_1-C_6)alkyl, (C_1-C_3)alkoxy, halogen, haloalkyl, haloalkoxy, acyl, amino, acylamino, thio or carboxylic or sulfonic acids and their derivatives.

It is preferred that Ar represents substituted or unsubstituted divalent phenylene, naphthylene, benzofuryl, indolyl, indolinyl, quinolinyl, azaindolyl, azaindolinyl, benzothiazolyl or benzoxazolyl.

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It is more preferred that Ar is represented by divalent phenylene or naphthylene, which may be unsubstituted or substituted by methyl, halomethyl, methoxy or halomethoxy groups.

Suitable R^4 includes hydrogen, lower alkyl groups such as methyl, ethyl or propyl; hydroxy, (C_1-C_3)alkoxy; halogen atom such as fluorine, chlorine, bromine, or iodine; aralkyl such as benzyl, phenethyl, which may be unsubstituted or substituted or R^4 together with R^5 represent a bond.

Suitable R^5 may be hydrogen, lower alkyl groups such as methyl, ethyl or propyl; hydroxy, (C_1-C_3)alkoxy; halogen atom such as fluorine, chlorine, bromine, iodine; acyl group such as linear or branched (C_2-C_{10})acyl group such as acetyl, propanoyl, butanoyl, pentanoyl, benzoyl and the like; aralkyl such as benzyl, phenethyl, which may be unsubstituted or substituted or together with R^4 forms a bond.

When R^4 or R^5 represents substituted aralkyl, the preferred substituents are hydroxy, halogen, alkyl and alkoxy.

It is preferred that R^4 and R^5 represent hydrogen atom or R^4 and R^5 together represent a bond.

Suitable groups represented by R^6 may be selected from hydrogen, substituted or unsubstituted, linear or branched (C_1-C_{16})alkyl, preferably (C_1-C_{12})alkyl group such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, pentyl, hexyl, octyl and the like; (C_3-C_7)cycloalkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like, the cycloalkyl group may be substituted; aryl group such as phenyl, naphthyl, the aryl group may be substituted; heteroaryl group such as pyridyl, thienyl, furyl and the like, the heteroaryl group may be substituted; heteroaralkyl group such as furanmethyl, pyridinemethyl, oxazolemethyl, oxazolethyl and the like, the heteroaralkyl group may be substituted; aralkyl group wherein the alkyl moiety may contain C_1-C_6 atoms such as benzyl and phenethyl etc, wherein the aryl moiety may be substituted; heterocyclyl group such as aziridinyl, pyrrolidinyl, piperidinyl and the like, the heterocyclyl group may be substituted; (C_1-C_6)alkoxy(C_1-C_6)alkyl group such as methoxymethyl, ethoxymethyl, methoxyethyl, ethoxypropyl and the like, the alkoxyalkyl group may be substituted; substituted or unsubstituted, linear or branched (C_2-C_{16})acyl group such as acetyl, propanoyl, butanoyl, benzoyl, octanoyl, decanoyl

and the like; (C_1-C_6)alkoxycarbonyl, the alkyl group may be substituted; aryloxycarbonyl such as phenoxycarbonyl, naphthyloxycarbonyl, the aryl group may be substituted; (C_1-C_6)alkylaminocarbonyl, the alkyl group may be substituted; arylaminocarbonyl such as PhNHCO, or naphthylaminocarbonyl, the aryl moiety may be substituted. The substituents may be selected from halogen, hydroxy, or nitro or unsubstituted or substituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aralkyl, aralkoxyalkyl, heterocyclyl, heteroaryl, heteroaralkyl, acyl, acyloxy, hydroxyalkyl, amino, acylamino, arylamino, aminoalkyl, aryloxy, alkoxycarbonyl, alkylamino, alkoxyalkyl, alkylthio, thioalkyl groups, carboxylic acid or its derivatives, or sulfonic acid or its derivatives .

Suitable groups represented by R^7 may be selected from hydrogen, substituted or unsubstituted, linear or branched (C_1-C_{16})alkyl, preferably (C_1-C_{12})alkyl group such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, pentyl, hexyl, octyl and the like; (C_3-C_7)cycloalkyl such as cyclopropyl, cyclopentyl, cyclohexyl and the like, the cycloalkyl group may be substituted; aryl group such as phenyl, naphthyl, the aryl group may be substituted; heteroaryl group such as pyridyl, thienyl, furyl and the like, the heteroaryl group may be substituted; heteroaralkyl group such as furanmethyl, pyridinemethyl, oxazolemethyl, oxazolethyl and the like, the heteroaralkyl group may be substituted; aralkyl group such as benzyl and phenethyl, the aralkyl group may be substituted; heterocyclyl group such as aziridinyl, pyrrolidinyl, piperidinyl and the like, the heterocyclyl group may be substituted. The substituents on R^7 may be selected from halogen, hydroxy, nitro or unsubstituted or substituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aralkyl, aralkoxyalkyl, heterocyclyl, heteroaryl, heteroaralkyl, acyl, acyloxy, hydroxyalkyl, amino, acylamino, arylamino, aminoalkyl, aryloxy, aralkoxy, alkoxycarbonyl, alkylamino, alkoxyalkyl, alkylthio, thioalkyl groups, carboxylic acid or its derivatives, or sulfonic acid or its derivatives.

Suitable groups represented by R^8 may be selected from hydrogen, substituted or unsubstituted, linear or branched (C_1-C_{16})alkyl, preferably (C_1-C_{12})alkyl; hydroxy (C_1-C_6)alkyl; aryl group such as phenyl, naphthyl; aralkyl group such as benzyl and phenethyl; heterocyclyl group such as aziridinyl, pyrrolidinyl, piperidinyl, and the like; heteroaryl group such as pyridyl, thienyl, furyl and the like; or heteroaralkyl group such as furanmethyl, pyridinemethyl, oxazolemethyl, oxazolethyl and the like.

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The cyclic structure formed by R^7 and R^8 together with the carbon atoms to which they are attached may be a substituted or unsubstituted 5 or 6 membered cyclic structure containing carbon atoms which may optionally contain one or two hetero-atoms selected from oxygen, nitrogen or sulfur. The cyclic structure may contain one or more double bonds.

Suitable ring structures formed by R^7 and R^8 together may be selected from pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, oxazolinyl, diazolinyl and the like.

Suitable substituents on the cyclic structure formed by R^7 and R^8 taken together may be selected from halogen, hydroxy, alkyl, oxo, aralkyl and the like.

For any R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 and Ar that may be substituted, the substituents are as defined above.

Suitable n is an integer ranging from 1 to 4, preferably n represents an integer 1 or 2.

The compounds of formula (I) where R^6 represents hydrogen atom and R^7 represents hydrogen or lower alkyl group have been claimed in our copending U.S. Patent Applications 08/777,627 and 08/884,816.

Pharmaceutically acceptable salts forming part of this invention include salts of the carboxylic acid moiety such as alkali metal salts like Li, Na, and K salts; alkaline earth metal salts like Ca and Mg salts; salts of organic bases such as lysine, arginine, guanidine, diethanolamine, choline, tromethamine and the like; ammonium or substituted ammonium salts and aluminum salts. Salts may include acid addition salts where appropriate which are, sulphates, nitrates, phosphates, perchlorates, borates, hydrohalides, acetates, tartrates, maleates, citrates, succinates, palmoates, methane-sulphonates, benzoates, salicylates, hydroxynaphthoates, benzenesulfonates, ascorbates, glycerophosphates, ketoglutarates and the like. Pharmaceutically acceptable solvates may be hydrates or comprising other solvents of crystallization such as alcohols.

Particularly useful compounds according to the present invention includes:

(±)-Ethyl 2-ethoxy-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl] methoxy]phenyl]propanoate;

(±)-2-Ethoxy-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl] methoxy] phenyl]propanoic acid;

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(±)-Sodium 2-ethoxy-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl] methoxy]phenyl]propanoate;

[2R, N(1S)] 2-ethoxy-3-[4-[[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl] ethoxy]phenyl] -N-(2-hydroxy-1-phenylethyl)propanamide;

[2S, N(1S)] 2-ethoxy-3-[4-[[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl] ethoxy]phenyl]-N-(2-hydroxy-1-phenylethyl)propanamide;

(+)-2-Ethoxy-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl] methoxy] phenyl]propanoic acid;

(-)-2-Ethoxy-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy] phenyl]propanoic acid;

(-)-Sodium 2-ethoxy-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl] methoxy]phenyl]propanoate;

(±)-(Morpholine-4-yl) 2-ethoxy-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl]propanamide;

(±)-2-Ethoxy-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl] methoxy] phenyl]-N-(2-fluorophenyl)propanamide;

(±)-Ethyl 2-methoxy-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl] methoxy]phenyl]propanoate;

(±)-2-Methoxy-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy] phenyl]propanoic acid;

(±)-Ethyl 2-propoxy-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl] methoxy]phenyl]propanoate;

(±)-2-Propoxy-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl] methoxy] phenyl]propanoic acid;

[2S, N(1S)] 2-propoxy-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl] methoxy]phenyl]-N-(2-hydroxy-1-phenylethyl)propanamide;

[2R, N(1S)] 2-Propoxy-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl] methoxy]phenyl]-N-(2-hydroxy-1-phenylethyl)propanamide;

(±)-Ethyl 2-(n-butoxy)-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl] methoxy]phenyl]propanoate;

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(±)-2-(n-Butoxy)-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl] methoxy] phenyl]propanoic acid;

(±)-Ethyl 2-(n-octyloxy)-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl] methoxy]phenyl]propanoate;

(±)-Ethyl 2-benzyloxy-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl] methoxy]phenyl] propanoate;

(±)-2-Benzyloxy-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl] methoxy] phenyl]propanoic acid;

(±)-Ethyl 2-phenoxy 3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl] methoxy]phenyl]propanoate;

(±)-2-Phenoxy-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl] methoxy] phenyl] propanoic acid;

(±)-Ethyl 2-(2-methoxyethoxy)-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl]propanoate;

(±)-2-(2-Methoxyethoxy)-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl] methoxy]phenyl]propanoic acid;

(±)-Ethyl 2-ethoxy-3-[4-[2-[2-ethyl-4-oxo-3,4-dihydro-3-quinazolinyl] ethoxy] phenyl]propanoate;

(±)-2-Ethoxy-3-[4-[2-[2-ethyl-4-oxo-3,4-dihydro-3-quinazolinyl] ethoxy] phenyl]propanoic acid;

[2R, N(1S)] 2-ethoxy-3-[4-[2-[2-ethyl-4-oxo-3,4-dihydro-3-quinazolinyl] ethoxy]phenyl]-N-(2-hydroxy-1-phenylethyl)propanamide;

[2S, N(1S)] 2-ethoxy-3-[4-[2-[2-ethyl-4-oxo-3,4-dihydro-3-quinazolinyl] ethoxy]phenyl]-N-(2-hydroxy-1-phenylethyl)propanamide;

(+) -2-Ethoxy-3-[4-[2-[2-ethyl-4-oxo-3,4-dihydro-3-quinazolinyl] ethoxy] phenyl]propanoic acid;

(-)-2-Ethoxy-3-[4-[2-[2-ethyl-4-oxo-3,4-dihydro-3-quinazolinyl] ethoxy] phenyl]propanoic acid;

(+)-Ethyl 2-ethoxy-3-[4-[2-[2-ethyl-4-oxo-3,4-dihydro-3-quinazolinyl] ethoxy] phenyl]propanoate;

(-)-Ethyl 2-ethoxy-3-[4-[2-[2-ethyl-4-oxo-3,4-dihydro-3-quinazolinyl] ethoxy] phenyl]propanoate;

(±)-Ethyl 2-ethoxy-3-[4-[2-[2-methyl-4-oxo-3,4-dihydro-3-quinazolinyl] ethoxy]phenyl]propanoate;

(±)-2-Ethoxy-3-[4-[2-[2-methyl-4-oxo-3,4-dihydro-3-quinazolinyl] ethoxy] phenyl]propanoic acid;

[2R, N(1S)] 2-ethoxy-3-[4-[2-[2-methyl-4-oxo-3,4-dihydro-3-quinazolinyl] ethoxy]phenyl]-N-(2-hydroxy-1-phenylethyl)propanamide;

[2S, N(1S)] 2-ethoxy-3-[4-[2-[2-methyl-4-oxo-3,4-dihydro-3-quinazolinyl] ethoxy]phenyl]-N-(2-hydroxy-1-phenylethyl)propanamide;

(+) -2-Ethoxy-3-[4-[2-[2-methyl-4-oxo-3,4-dihydro-3-quinazolinyl] ethoxy] phenyl]propanoic acid;

(-)-2-Ethoxy-3-[4-[2-[2-methyl-4-oxo-3,4-dihydro-3-quinazolinyl] ethoxy] phenyl]propanoic acid;

(+)-Ethyl 2-ethoxy-3-[4-[2-[2-methyl-4-oxo-3,4-dihydro-3-quinazolinyl] ethoxy]phenyl]propanoate;

(-)-Ethyl-2-ethoxy-3-[4-[2-[2-methyl-4-oxo-3,4-dihydro-3-quinazolinyl] ethoxy]phenyl]propanoate;

(±)-Ethyl 2-ethoxy-3-[4-[2-[4-oxo-3,4-dihydro-3-quinazolinyl] ethoxy] phenyl]propanoate;

(±)-2-Ethoxy-3-[4-[2-[4-oxo-3,4-dihydro-3-quinazolinyl]ethoxy]p phenyl] propanoic acid;

(±)-Ethyl 2-phenoxy-3-[4-[2-[2-ethyl-4-oxo-3,4-dihydro-3-quinazolinyl] ethoxy]phenyl]propanoate;

(±)-2-Phenoxy-3-[4-[2-[2-ethyl-4-oxo-3,4-dihydro-3-quinazolinyl] ethoxy] phenyl]propanoic acid;

(±)-Ethyl 2-phenoxy-3-[4-[2-[2-methyl-4-oxo-3,4-dihydro-3-quinazolinyl] ethoxy]phenyl]propanoate;

(±)-2-Phenoxy-3-[4-[2-[2-methyl-4-oxo-3,4-dihydro-3-quinazolinyl] ethoxy] phenyl]propanoic acid;

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(±)-Ethyl 2-ethoxy-3-[4-[2-[2-ethyl-4-methyl-6-oxo-1-pyrimidinyl]ethoxy] phenyl]propanoate;

(±)-2-Ethoxy-3-[4-[2-[2-ethyl-4-methyl-6-oxo-1-pyrimidinyl] ethoxy] phenyl] propanoic acid;

(±)-Ethyl 2-ethoxy-3-[4-[[3-phenyl-4-oxo-3,4-dihydro-2-quinazolinyl] methoxy]phenyl]propanoate;

(±)-2-Ethoxy-3-[4-[2-[2-ethyl-4-methyl-6-oxo-1-pyrimidinyl] ethoxy] phenyl] propanoic acid;

(±)-Ethyl 2-ethoxy-3-[4-[[3-phenyl-4-oxo-3,4-dihydro-2-quinazolinyl] methoxy]phenyl]propanoate;

(±)-2-Ethoxy-3-[4-[[3-phenyl-4-oxo-3,4-dihydro-2-quinazolinyl] methoxy] phenyl]propanoic acid;

(±)-Ethyl 2-ethoxy-3-[4-[[3-methyl-4-oxo-3,4-dihydro-6,7-dimethoxy-2-quinazolinyl]methoxy]phenyl]propanoate;

(±)- 2-Ethoxy-3-[4-[[3-methyl-4-oxo-3,4-dihydro-6,7-dimethoxy-2-quinazolinyl]methoxy] phenyl]propanoic acid;

(±)-Ethyl 2-ethoxy-3-[4-[[3-(4-methylphenyl)-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy] phenyl]propanoate;

(±)-2-Ethoxy-3-[4-[[3-(4-methylphenyl)-4-oxo-3,4-dihydro-2-quinazolinyl] ethoxy] phenyl]propanoic acid;

(±)-Ethyl 2-ethoxy-3-[4-[[3-(4-methoxyphenyl)-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy] phenyl]propanoate;

(±)-2-Ethoxy-3-[4-[[3-(4-methoxyphenyl)-4-oxo-3,4-dihydro-2-quinazolinyl] methoxy]phenyl]propanoic acid;

(±)-Ethyl 2-ethoxy-3-[4-[[3-benzyl-4-oxo-3,4-dihydro-2-quinazolinyl] methoxy]phenyl]propanoate;

(±)-2-Ethoxy-3-[4-[[3-benzyl-4-oxo-3,4-dihydro-2-quinazolinyl] methoxy] phenyl]propanoic acid;

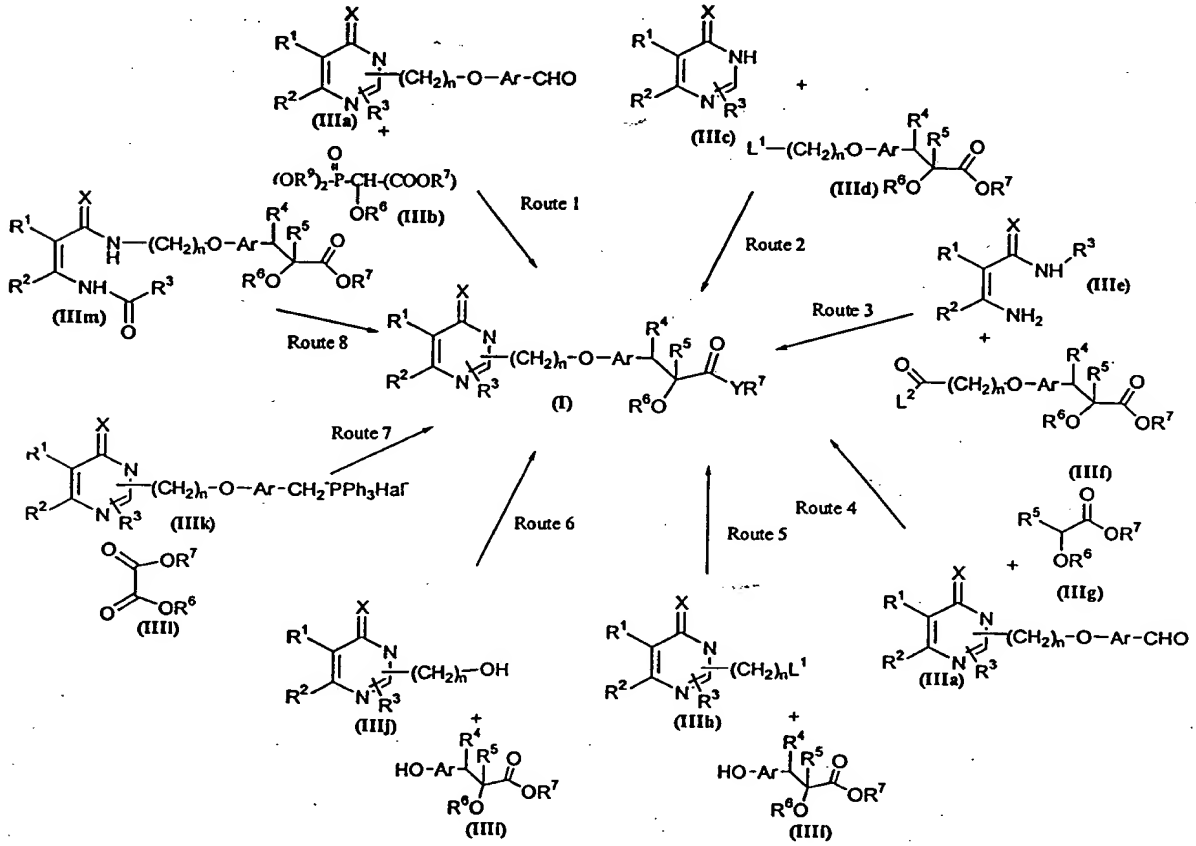
(±)-Ethyl 2-ethoxy-3-[4-[[3-(3-chlorophenyl)-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl]propanoate;

(±)-2-Ethoxy-3-[4-[[3-(3-chlorophenyl)-4-oxo-3,4-dihydro-2-quinazolinyl] methoxy]phenyl]propanoic acid;

(±)-Ethyl 2-ethoxy-3-[4-[[3-(3-chloro-4-fluorophenyl)-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl]propanoate; and

(±)-2-Ethoxy-3-[4-[[3-(3-chloro-4-fluorophenyl)-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl]propanoic acid.

According to a feature of the present invention, the compound of general formula (I) where R^4 and R^5 together represent a bond , Y represents an oxygen atom, R^1, R^2, R^3, R^6, R^7, X, n and Ar are as defined earlier, can be prepared by any of the following routes shown in Scheme-I below.



Scheme - I

Route (1): The reaction of a compound of the general formula (IIIa) where all symbols are as defined earlier with a compound of formula (IIIb) where R^6 and R^7 are

as defined earlier excluding hydrogen and R^9 represents (C_1-C_6)alkyl, to yield compound of general formula (I) where R^6 and R^7 are as defined above excluding hydrogen and all other symbols are as defined above may be carried out in the presence of a base such as alkali metal hydrides like NaH, or KH or organolithiums like CH_3Li, BuLi and the like or alkoxides such as NaOMe, NaOEt, K^+BuO^- or mixtures thereof. The reaction may be carried out in the presence of solvents such as THF, dioxane, DMF, DMSO, DME and the like or mixtures thereof. HMPA may be used as a cosolvent. The reaction temperature may range from -78°C to 50°C, preferably at a temperature in the range of -10°C to 30°C. The reaction is more effective under anhydrous conditions. The compound of general formula (IIIb) may be prepared by Arbuzov reaction.

Alternatively, the compound of formula (I) may be prepared by reacting the compound of formula (IIIa) where all symbols are as defined earlier with Wittig reagents such as $Hal^-Ph_3P^+CH\text{-}(OR^6)CO_2R^7$ under similar reaction conditions as described above.

Route (2): The reaction of a compound of general formula (IIIc) where all symbols are as defined earlier with a compound of general formula (IIId) where R^4 and R^5 together represent a bond and all symbols are as defined earlier and L^1 is a leaving group such as halogen atom, p-toluenesulfonate, methanesulfonate, trifluoromethane-sulfonate and the like, preferably a halogen atom to produce a compound of general formula (I) where $-(CH_2)_n-$ linker group is attached through the nitrogen atom and all other symbols are as defined above may be carried out in the presence of solvents such as DMSO, DMF, DME, THF, dioxane, ether and the like or a combination thereof. The reaction may be carried out in an inert atmosphere which may be maintained by using inert gases such as N_2, Ar, or He. The reaction may be effected in the presence of a base such as alkalis like sodium hydroxide, or potassium hydroxide, alkali metal carbonates like sodium carbonate, or potassium carbonate; alkali metal hydrides such as sodium hydride or potassium hydride; organometallic bases like n-butyl lithium, alkali metal amides like sodamide or mixtures thereof. The amount of base may range from 1 to 5 equivalents, based on the amount of the compound of formula (IIIc), preferably the amount of base ranges from 1 to 3 equivalents. Phase transfer catalysts such as tetraalkylammonium halide or hydroxide may be added. Additives such as

alkali metal halides such as LiBr may be added. The reaction may be carried out at a temperature in the range of 0°C to 150°C, preferably at a temperature in the range of 15°C to 100°C. The duration of the reaction may range from 0.25 to 48 hours, preferably from 0.25 to 12 hours.

Route (3): The reaction of compound of general formula (IIIe) with a compound of general formula (IIIf) where R^4, R^5 together represent a bond, L^2 is halogen, -OH, $-OR^{10}$, $-O-C(=O)-OR^{10}$, where R^{10} is (C_1-C_5)alkyl and other symbols are as defined earlier, to produce a compound of general formula (I) where $-(CH_2)_n-$ linker group is attached through the carbon atom and all other symbols are as defined above may be carried out in the presence of solvents such as xylene, toluene, THF, dioxane, acetic acid, DMF, DMSO and the like or mixtures thereof. The reaction may be carried out in an inert atmosphere which may be maintained by using inert gases such as N_2, Ar or He. The reaction may be carried out at a temperature in the range of 50°C to 200°C, preferably at a temperature in the range of 60° C to 180°C. The reaction may be effected in the presence or in absence of a base or an acid. The nature of the base or the acid is not critical. Examples of such bases include organic bases such as pyridine, lutidine, triethyl amine, diisopropylethyl amine and the like, and metal carbonates such as K_2CO_3, or Na_2CO_3. Examples of acids include organic acids such as AcOH, C_2H_5COOH, butyric acid, trifluoroacetic acid, p-toluenesulfonic acid, benzenesulfonic acid and the like, and mineral acids such as HCl, HBr etc. The duration of the reaction may range from 0.25 to 48 hours, preferably from 0.50 to 18 hours. This process is preferably used for the preparation of a compound of formula (I) wherein R^1 and R^2 together represent a cyclic structure defined earlier.

Route (4): The reaction of a compound of the general formula (IIIa) where all symbols are as defined earlier, with a compound of formula (IIIg) where R^5 is hydrogen and all other symbols are as defined earlier may be carried out in the presence of a base. The nature of the base is not critical. Any base normally employed for aldol condensation reaction may be employed; bases like metal hydride such as NaH, or KH; metal alkoxides such as NaOMe, t-BuO^-K^+, or NaOEt; or metal amides such as $LiNH_2$, $LiN(ipr)_2$ may be used. Aprotic solvents such as THF, ether, dioxane

may be used. The reaction may be carried out in an inert atmosphere which may be maintained by using inert gases such as N_2, Ar, or He and the reaction is more effective under anhydrous conditions. Temperature in the range of -80°C to 35°C may be used. The β-hydroxy product initially produced may be dehydrated under conventional dehydration conditions such as treating with PTSA in solvents such as benzene or toluene. The nature of solvent and dehydrating agent is not critical. Temperature in the range of 20°C to reflux temperature of the solvent used may be employed, preferably at reflux temperature of the solvent by continuous removal of water using a Dean Stark water separator.

Route (5): The reaction of compound of formula (IIIh) where all symbols are as defined earlier and L^1 represents a leaving group such as halogen atom, p-toluene-sulfonate, methanesulfonate, trifluoromethanesulfonate and the like, preferably a halogen atom with compound of formula (IIIi) where R^4 and R^5 together represent a bond and all other symbols are as defined earlier to produce a compound of the formula (I) defined above may be carried out in the presence of aprotic solvents such as THF, DMF, DMSO, DME and the like or mixtures thereof. The reaction may be carried out in an inert atmosphere which may be maintained by using inert gases such as N_2, Ar, or He. The reaction may be effected in the presence of a base such as K_2CO_3, Na_2CO_3 or NaH or mixtures thereof. Acetone may be used as solvent when Na_2CO_3 or K_2CO_3 is used as a base. The reaction temperature may range from 0°C-120°C, preferably at a temperature in the range of 30°C-100°C. The duration of the reaction may range from 1 to 24 hours, preferably from 2 to 12 hours. The compound of formula (IIIi) can be prepared according to known procedure by a Wittig Horner reaction between the hydroxy protected aryl aldehyde such as benzyloxyaryl aldehyde and compound of formula (IIIb), followed by deprotection.

Route (6): The reaction of compound of general formula (IIIj) where all symbols are as defined earlier with a compound of general formula (IIIi) where R^4 and R^5 together represent a bond and all symbols are as defined earlier may be carried out using suitable coupling agents such as dicyclohexyl urea, or triarylphosphine/ dialkylazadicarboxylate such as PPh_3/DEAD and the like. The reaction may be carried out in the presence of solvents such as THF, DME, CH_2Cl_2, $CHCl_3$, toluene,

acetonitrile, carbon tetrachloride and the like. The inert atmosphere may be maintained by using inert gases such as N_2, Ar, or He. The reaction may be effected in the presence of DMAP, HOBT and they may be used in the range of 0.05 to 2 equivalents, preferably 0.25 to 1 equivalents. The reaction temperature may be in the range of 0°C to 100°C, preferably at a temperature in the range of 20°C to 80°C. The duration of the reaction may range from 0.5 to 24 hours, preferably from 6 to 12 hours.

Route 7: The reaction of a compound of formula (IIIk) where all symbols are as defined earlier with a compound of formula (IIIl) where $R^6 = R^7$ and are as defined earlier excluding hydrogen, to produce a compound of the formula (I) where R^4 and R^5 together represent a bond may be carried out neat in the presence of a base such as alkali metal hydrides like NaH, KH or organolithiums like CH_3Li, BuLi and the like or alkoxides such as NaOMe, NaOEt, $t\text{-BuO}^-K^+$ and the like or mixtures thereof. The reaction may be carried out in the presence of aprotic solvents such as THF, dioxane, DMF, DMSO, DME and the like or mixtures thereof. HMPA may be used as cosolvent. The reaction temperature may range from -78°C to 100°C, preferably at a temperature in the range of -10°C to 50°C.

Route 8: The cyclization of compound of general formula (IIIm), where R^4 and R^5 together represent a bond, R^7 is as defined earlier excluding hydrogen atom and all other symbols are as defined earlier to produce a compound of general formula (I), where $-(CH_2)n-$ linker group is attached through nitrogen atom and all other symbols are as defined earlier may be carried out neat or in the presence of solvents such as xylene, toluene, THF, dioxane, acetic acid, DMF, DMSO and the like or mixtures thereof. The reaction may be carried out in an inert atmosphere which may be maintained by using inert gases such as N_2, Ar or He. The reaction may be carried out at a temperature in the range of 50°C to 200°C, preferably at a temperature in the range of 60°C to 180°C. The reaction may be effected in the presence or in absence of a base or an acid. The nature of the base or the acid is not critical. Examples of such bases include organic bases such as pyridine, lutidine, triethyl amine, diisopropylethyl amine and the like; metal carbonates such as K_2CO_3, or Na_2CO_3. Examples of acids include organic acids such as AcOH, C_2H_5COOH, butyric acid, trifluoroacetic acid, p-toluenesulfonic acid, benzenesulfonic acid and the like, or

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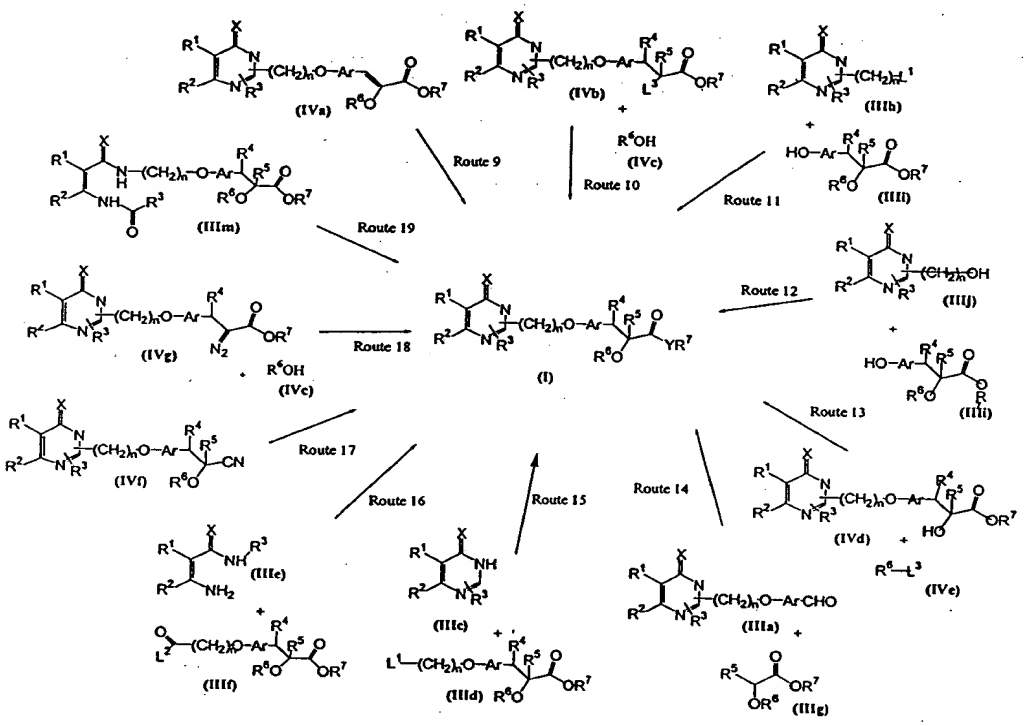
mineral acids such as HCl, HBr etc. The duration of the reaction may range from 0.25 to 48 hours, preferably from 0.50 to 18 hours. This process is preferably used for the preparation of a compound of formula (I) wherein R^1 and R^2 together represent a cyclic structure as defined earlier.

In yet another embodiment of the present invention, the compound of the general formula (I) where R^4 represents hydrogen atom, hydroxy, alkoxy, halogen, lower alkyl, or unsubstituted or substituted aralkyl group; R^5 represents hydrogen, hydroxy, alkoxy, halogen, lower alkyl group, acyl, or unsubstituted or substituted aralkyl; and R^1, R^2, R^3, R^6, R^7, X, n and Ar are as defined earlier and Y represents oxygen atom can be prepared by one or more of the processes shown in Scheme-II below.



Scheme - II

Route 9: The reduction of compound of the formula (IVa) which represents a compound of formula (I) where R^4 and R^5 together represent a bond and Y represents oxygen atom and all other symbols are as defined earlier, obtained as described

earlier(Scheme-I), to yield a compound of the general formula (I) where R^4 and R^5 each represent hydrogen atom and all symbols are as defined earlier, may be carried out in the presence of gaseous hydrogen and a catalyst such as Pd/C, Rh/C, Pt/C, and the like. Mixtures of catalysts may be used. The reaction may also be conducted in the presence of solvents such as dioxane, acetic acid, and ethyl acetate, or alcohol such as methanol, ethanol and the like. A pressure between atmospheric pressure and 80 psi may be employed. The catalyst may be preferably 5-10 % Pd/C and the amount of catalyst used may range from 5-100% w/w. The reaction may also be carried out by employing metal solvent reduction such as magnesium in alcohol or sodium amalgam in alcohol, preferably methanol. The hydrogenation may be carried out in the presence of metal catalysts containing chiral ligands to obtain a compound of formula (I) in optically active form. The metal catalyst may contain Rhodium, Ruthenium, Indium and the like. The chiral ligands may preferably be chiral phosphines such as optically pure enantiomers of 2,3-bis(diphenylphosphino)butane, 1,2-bis(diphenylphosphino)ethane, 1,2-bis(2-methoxyphenyl phenylphosphino)ethane, 2,3-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino) butane and the like. Any suitable chiral catalyst may be employed which would give required optical purity of the product (I) (Ref: Principles of Asymmetric Synthesis, Tetrahedron Series Vol 14, pp311-316, Ed. Baldwin J. E.).

Route 10: The reaction of compound of formula (IVb) where R^7 is as defined earlier excluding hydrogen all other symbols are as defined earlier and L^3 is a leaving group such as halogen atom with an alcohol of general formula (IVc), where R^6 is as defined earlier excluding hydrogen to produce a compound of the formula (I) defined earlier may be carried out in the presence of solvents such as THF, DMF, DMSO, DME and the like or mixtures thereof. The reaction may be carried out in an inert atmosphere which may be maintained by using inert gases such as N_2, Ar, or He. The reaction may be effected in the presence of a base such as KOH, NaOH, NaOMe, NaOEt, t-BuO^-K^+ or NaH or mixtures thereof. Phase transfer catalysts such as tetraalkylammonium halides or hydroxides may be employed. The reaction temperature may range from 20°C-120°C, preferably at a temperature in the range of 30°C-100°C. The duration of the reaction may range from 1 to 12 hours, preferably from 2 to 6 hours. The compound of general formula (IVb) where R^7 represents

hydrogen or lower alkyl group and its preparation has been disclosed in the copending U.S. Patent Application Nos. 08/777,627 and 08/884,816.

Route 11: The reaction of compound of formula (IIIh) defined earlier with compound of formula (IIIi) where all symbols are as defined earlier to produce a compound of the formula (I) defined above, may be carried out in the presence of solvents such as THF, DMF, DMSO, DME and the like or mixtures thereof. The reaction may be carried out in an inert atmosphere which is maintained by using inert gases such as N_2, Ar or He. The reaction may be effected in the presence of a base such as K_2CO_3, Na_2CO_3 or NaH or mixtures thereof. Acetone may be used as a solvent when K_2CO_3 or Na_2CO_3 is used as a base. The reaction temperature may range from 20°C-120°C, preferably at a temperature in the range of 30°C-80°C. The duration of the reaction may range from 1 to 24 hours, preferably from 2 to 12 hours. The compound of formula (IIIi) may be prepared by Wittig Horner reaction between the protected hydroxyaryl aldehyde and compound of formula (IIIb) followed by reduction of the double bond and deprotection. Alternatively, the compound of formula (IIIi) may be prepared by following a procedure disclosed in WO 94/01420.

Route 12: The reaction of compound of general formula (IIIj) defined earlier with a compound of general formula (IIIi) where all symbols are as defined above may be carried out using suitable coupling agents such as dicyclohexyl urea, triarylphosphine/dialkylazadicarboxylate such as PPh_3/DEAD and the like. The reaction may be carried out in the presence of solvents such as THF, DME, CH_2Cl_2, $CHCl_3$, toluene, acetonitrile, carbon tetrachloride and the like. The inert atmosphere may be maintained by using inert gases such as N_2, Ar, or He. The reaction may be effected in the presence of DMAP, HOBT and they may be used in the range of 0.05 to 2 equivalents, preferably 0.25 to 1 equivalents. The reaction temperature may be in the range of 0°C to 100°C, preferably at a temperature in the range of 20°C to 80°C. The duration of the reaction may range from 0.5 to 24 hours, preferably from 6 to 12 hours.

Route 13: The reaction of compound of formula (IVd) which represents a compound of formula (I) where all symbols are as defined above with a compound of formula (IVe) where R^6 is as defined earlier excluding hydrogen and L^3 is a halogen atom may be carried out in the presence of solvents such as THF, DMF, DMSO, DME

and the like. The inert atmosphere may be maintained by using inert gases such as N_2, Ar or He. The reaction may be effected in the presence of a base such as KOH, NaOH, NaOMe, t-BuO^-K^+, NaH and the like. Phase transfer catalyst such as tetraalkylammonium halides or hydroxides may be employed. The reaction temperature may range from 20°C to 150°C, preferably at a temperature in the range of 30°C to 100°C. The duration of the reaction may range from 1 to 24 hours, preferably from 2 to 6 hours.

The compound of formula (IVd) where R^7 represents hydrogen or lower alkyl group and its preparation has been disclosed in the copending U.S. Patent Application Nos. 08/777,627 and 08/884,816. The compound of formula (IVd) represents a compound of formula (I) where R^6 represents hydrogen atom and all other symbols are as defined earlier.

Route 14: The reaction of a compound of the general formula (IIIa) as defined above with a compound of formula (IIIg) where all symbols are as defined earlier may be carried out under conventional conditions. The base is not critical. Any base normally employed for aldol condensation reaction may be employed, metal hydride such as NaH, or KH; metal alkoxides such as NaOMe, t-BuO^-K^+, or NaOEt; or metal amides such as $LiNH_2$, or $LiN(iPr)_2$. Aprotic solvent such as THF may be used. Inert atmosphere may be employed such as argon and the reaction is more effective under anhydrous conditions. Temperature in the range of -80°C to 25°C may be used. The β-hydroxy aldol product may be dehydroxylated using conventional methods, conveniently by ionic hydrogenation technique such as by treating with a trialkyl silane in the presence of an acid such as trifluoroacetic acid. Solvent such as CH_2Cl_2 may be used. Favorably, reaction proceeds at 25°C. Higher temperature may be employed if the reaction is slow.

Route 15: The reaction of a compound of general formula (IIIc) where all symbols are as defined earlier with a compound of general formula (IIId) where L^1 is a leaving group such as halogen atom, p-toluenesulfonate, methanesulfonate, trifluoromethanesulfonate and the like, preferably a halogen atom and all other symbols are as defined earlier to produce a compound of general formula (I) where $-(CH_2)_n-$ is attached through nitrogen atom and all other symbols are as defined above may be

carried out in the presence of solvents such as DMSO, DMF, DME, THF, dioxane, ether and the like or a combination thereof. The reaction may be carried out in an inert atmosphere which may be maintained by using inert gases such as N_2, Ar, or He. The reaction may be effected in the presence of a base such as alkalis like sodium hydroxide, potassium hydroxide, alkali metal carbonates like sodium carbonate, or potassium carbonate; alkali metal hydrides such as sodium hydride or potassium hydride; organometallic bases like n-butyl lithium, alkali metal amides like sodamide or mixtures thereof. The amount of base may range from 1 to 5 equivalents, based on the amount of the compound of formula (IIIc), preferably the amount of base ranges from 1 to 3 equivalents. Additives such as alkali metal halides such as LiBr may be added. The reaction may be carried out at a temperature in the range of 0°C to 150°C, preferably at a temperature in the range of 15°C to 100°C. The duration of the reaction may range from 0.25 to 24 hours, preferably from 0.25 to 12 hours.

Route 16: The reaction of compound of general formula (IIIe) as defined earlier with a compound of general formula (IIIf) where L^2 is a leaving group such as halogen, -OH, $-OR^{10}$, or $-O-C(=O)-OR^{10}$, where R^{10} is (C_1-C_5)alkyl and all other symbols are as defined earlier, to produce a compound of general formula (I) where $-(CH_2)_n-$ is attached through carbon atom and all other symbols are as defined above may be carried out in neat or in the presence of solvents such as xylene, toluene, THF, dioxane, acetic acid, DMF, DMSO and the like or mixtures thereof. The reaction may be carried out in an inert atmosphere which may be maintained by using inert gases such as N_2, Ar or He. The reaction may be carried out at a temperature in the range of 50°C to 200°C, preferably at a temperature in the range of 60°C to 180°C. The reaction may be effected in the presence or in absence of a base or an acid. The nature of the base or the acid is not critical. Examples of such bases include organic bases such as pyridine, lutidine, triethyl amine, diisopropylethyl amine and the like; metal carbonates such as K_2CO_3, or Na_2CO_3. Examples of acids include organic acids such as AcOH, C_2H_5COOH, butyric acid, trifluoroacetic acid, p-toluenesulfonic acid, benzenesulfonic acid and the like, mineral acids such as HCl, or HBr etc. The duration of the reaction may range from 0.25 to 48 hours, preferably from 0.50 to 18

hours. This process is preferably used for the preparation of a compound of formula (I) wherein R^1 and R^2 together represent a cyclic structure defined earlier.

Route 17: The conversion of compound of formula (IVf) where all symbols are as defined earlier to a compound of formula (I) may be carried out either in the presence of base or acid and the selection of base or acid is not critical. Any base normally used for hydrolysis of nitrile to acid may be employed, metal hydroxides such as NaOH, KOH in an aqueous solvent or any acid normally used for hydrolysis of nitrile to ester may be employed such as dry HCl in an excess of alcohol such as methanol, ethanol, propanol etc. The reaction may be carried out at a temperature in the range of 0°C to reflux temperature of the solvent used, preferably at a temperature in the range of 25°C to reflux temperature of the solvent used. The duration of the reaction may range from 0.25 to 48 hrs.

Route 18: The reaction of a compound of formula (IVg) where R^7 is as defined earlier excluding hydrogen and all symbols are as defined earlier with a compound of formula (IVc) where R^6 is as defined earlier excluding hydrogen to produce a compound of formula (I) (by a rhodium carbenoid mediated insertion reaction) may be carried out in the presence of rhodium (II) salts such as rhodium (II) acetate. The reaction may be carried out in the presence of solvents such as benzene, toluene, dioxane, ether, THF and the like or a combination thereof or when practicable in the presence of R^6OH as solvent at any temperature providing a convenient rate of formation of the required product, generally at an elevated temperature, such as reflux temperature of the solvent. The inert atmosphere may be maintained by using inert gases such as N_2, Ar, or He. The duration of the reaction may be range from 0.5 to 24 h, preferably from 0.5 to 6 h.

Route 19: The cyclization of compound of general formula (IIIm), where R^7 is as defined earlier excluding hydrogen atom and all other symbols are as defined above to produce a compound of general formula (I), where $-(CH_2)n-$ linker group is attached through nitrogen atom and all other symbols are as defined earlier may be carried out neat or in the presence of solvents such as xylene, toluene, THF, dioxane, acetic acid, DMF, DMSO and the like or mixtures thereof. The reaction may be carried out in an inert atmosphere which may be maintained by using inert gases such as N_2, Ar or He. The reaction may be carried out at a temperature in the range of 50°C

to 200°C, preferably at a temperature in the range of 60°C to 180°C. The reaction may be effected in the presence or in absence of a base or an acid. The nature of the base or the acid is not critical. Examples of such bases include organic bases such as pyridine, lutidine, triethyl amine, diisopropylethyl amine and the like; or metal carbonates such as K_2CO_3, or Na_2CO_3. Examples of acids include organic acids such as AcOH, C_2H_5COOH, butyric acid, trifluoroacetic acid, p-toluenesulfonic acid, benzenesulfonic acid and the like, or mineral acids such as HCl, HBr etc. The duration of the reaction may range from 0.25 to 48 hours, preferably from 0.50 to 18 hours. This process is preferably used for the preparation of a compound of formula (I) wherein R^1 and R^2 together represent a cyclic structure as defined earlier.

The compound of general formula (I) where R^7 represents hydrogen atom may be prepared by hydrolysing using conventional methods, a compound of formula (I) where R^7 represents all groups defined earlier except hydrogen. The hydrolysis may be carried out in the presence of a base such as Na_2CO_3 and a suitable solvent such as methanol, ethanol and the like or mixtures thereof. The reaction may be carried out at a temperature in the range of 20-40°C, preferably at 25-30°C. The reaction time may range from 2 to 12 h, preferably from 4 to 8 h.

The compound of general formula (I) where Y represents oxygen and R^7 represents hydrogen or lower alkyl gorup is as defined earlier may be converted to compound of formula (I), where Y represents NR^8 by reaction with appropriate amines of formula NHR^7R^8 where R^7 and R^8 are as defined earlier. Alternatively, the compound of formula (I) where YR^7 represents OH may be converted to acid halide, preferably YR^7 = Cl, by reacting with appropriate reagents such as oxalyl chloride, thionyl chloride and the like, followed by treatment with amines of formula NHR^7R^8 where R^7 and R^8 are as defined earlier. Alternatively, mixed anhydrides may be prepared from compound of formula (I) where YR^7 represents OH and all other symbols are as defined earlier by treating with acid halides such acetyl chloride, acetyl bromide, pivaloyl chloride, dichlorobenzoyl chloride and the like. The reaction may be carried out in the presence of suitable base such as pyridine, triethylamine, diiso-propyl ethyl amine and the like. Solvents such as halogenated hydrocarbons like $CHCl_3$, or CH_2Cl_2; hydrocarbons such as benzene, toluene, xylene and the like may be

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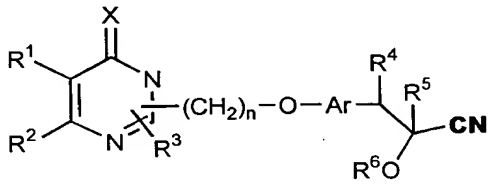
used. The reaction may be carried out at a temperature in the range of –40°C to 40°C, preferably 0°C to 20°C. The acid halide or mixed anhydride thus prepared may further be treated with appropriate amines of formula NHR^7R^8 where R^7 and R^8 are as defined earlier.

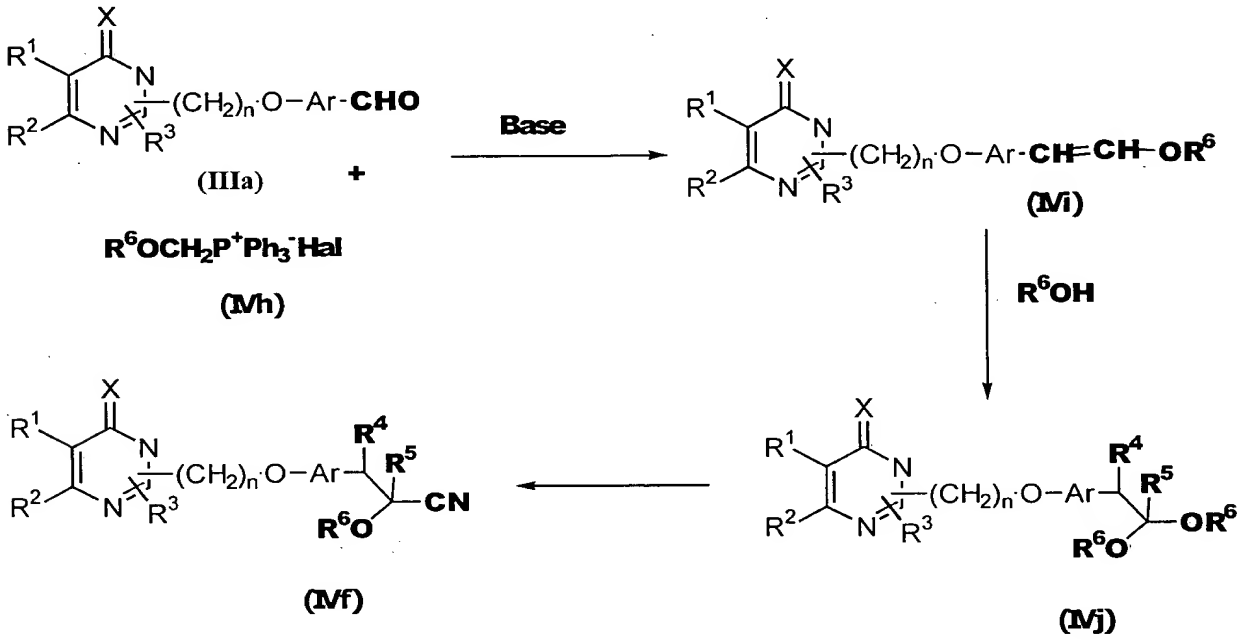
In another embodiment of the present invention there is provided the novel intermediates of formula (IVf)



(IVf)

where X represents O or S; the groups R^1, R^2 and group R^3 when present on carbon atom, may be same or different and represent hydrogen, halogen, hydroxy, nitro, cyano, formyl or unsubstituted or substituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, acyloxy, hydroxyalkyl, amino, acylamino, alkylamino, arylamino, aralkylamino, aminoalkyl, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, carboxylic acid or its derivatives, or sulfonic acid or its derivatives; or R^1, R^2 along with the adjacent atoms to which they are attached may also form a 5-6 membered substituted or unsubstituted cyclic structure containing carbon atoms with one or more double bonds, which may optionally contain one or more heteroatoms selected from oxygen, nitrogen and sulfur; R^3 when attached to nitrogen atom represents hydrogen, hydroxy, formyl or unsubstituted or substituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aralkyl, heterocyclyl, heteroaryl, heteroaralkyl, acyl, acyloxy, hydroxyalkyl, amino, acylamino, alkylamino, arylamino, aralkylamino, aminoalkyl, aryloxy, aralkoxy, heteroaryloxy, heteroaralkoxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl groups, carboxylic acid derivatives, or sulfonic acid derivatives; the linking group represented by $-(CH_2)_n-O-$ may be attached either through nitrogen atom or through carbon atom where n is an integer ranging from 1 – 4; Ar represents an unsubstituted or substituted divalent single or fused aromatic or heterocyclic group; R^4 represents hydrogen atom,

hydroxy, alkoxy, halogen, lower alkyl, unsubstituted or substituted aralkyl group or forms a bond together with the adjacent group R^5; R^5 represents hydrogen, hydroxy, alkoxy, halogen, lower alkyl group, acyl, unsubstituted or substituted aralkyl or R^5 forms a bond together with R^4; R^6 may be hydrogen, or unsubstituted or substituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, alkoxyalkyl, alkoxycarbonyl, aryloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, acyl, heterocyclyl, hetero-aryl, heteroaralkyl groups and a process for its preparation and its use in the preparation of β-aryl-α-oxysubstituted alkylcarboxylic acids is provided (Scheme-III).



Scheme III

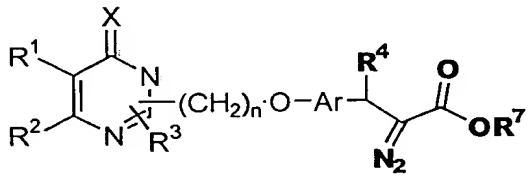
The reaction of a compound of formula (IIIa) where all symbols are as defined earlier with a compound of formula (IVh) where R^6 is as defined earlier excluding hydrogen and Hal represent a halogen atom such as Cl, Br, or I to produce a compound of formula (IVi) where all symbols are defined earlier and R^6 is as defined earlier excluding hydrogen may be carried out under conventional conditions in the presence of a base. The base is not critical. Any base normally employed for Wittig reaction may be employed, metal hydride such as NaH, or KH; metal alkoxides such as NaOMe, K^tBuO^-, or NaOEt; or metal amides such as $LiNH_2$, or $LiN(iPr)_2$. Aprotic solvent such as THF, DMSO, dioxane, DME and the like may be used. Mixture of solvents may be used. HMPA may be used as cosolvent. Inert atmosphere may be

employed such as argon and the reaction is more effective under anhydrous conditions. Temperature in the range of -80°C to 100°C may be used.

The compound of formula (IVi) where all symbols are as defined earlier and R^6 is as defined earlier excluding hydrogen may be converted to a compound of formula (IVj) where R^4 and R^5 represent H atoms, R^6 is as defined earlier excluding hydrogen and all other symbols are as defined earlier, by treating with an alcohol under anhydrous conditions in the presence of a strong anhydrous acid such as p-toluene-sulfonic acid.

The compound of formula (IVj) defined above upon treatment with trialkyl-silyl cyanide such as trimethylsilyl cyanide produces a compound of formula (IVf) where R^4 and R^5 represent H atoms, R^6 is as defined earlier excluding hydrogen and all other symbols are as defined earlier.

In still another embodiment of the present invention there is provided the novel intermediates of formula (IVg)

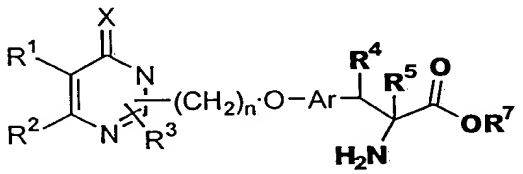


(IVg)

where X represents O or S; the groups R^1, R^2 and group R^3 when present on carbon atom, may be same or different and represent hydrogen, halogen, hydroxy, nitro, cyano, formyl or unsubstituted or substituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, hetero-aralkyl, heteroaryloxy, heteroaralkoxy, acyl, acyloxy, hydroxyalkyl, amino, acylamino, alkylamino, arylamino, aralkylamino, aminoalkyl, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, carboxylic acid or its derivatives, or sulfonic acid or its derivatives; or R^1, R^2 along with the adjacent atoms to which they are attached may also form a 5-6 membered substituted or unsubstituted cyclic structure containing carbon atoms with one or more double bonds, which may optionally contain one or more heteroatoms selected from oxygen, nitrogen and sulfur; R^3 when attached to nitrogen atom represents hydrogen, hydroxy, formyl or unsubstituted or substituted groups selected from alkyl, cycloalkyl, alkoxy, cyclo-

alkoxy, aryl, aralkyl, heterocyclyl, heteroaryl, heteroaralkyl, acyl, acyloxy, hydroxyalkyl, amino, acylamino, alkylamino, arylamino, aralkylamino, aminoalkyl, aryloxy, aralkoxy, heteroaryloxy, heteroaralkoxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl groups, carboxylic acid derivatives, or sulfonic acid derivatives; the linking group represented by $-(CH_2)_n-O-$ may be attached either through nitrogen atom or through carbon atom where n is an integer ranging from 1 – 4; Ar represents an unsubstituted or substituted divalent single or fused aromatic or heterocyclic group; R^4 represents hydrogen atom, hydroxy, alkoxy, halogen, lower alkyl, or unsubstituted or substituted aralkyl; R^7 may be hydrogen or unsubstituted or substituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, or heteroaralkyl groups and a process for its preparation and its use in the preparation of β-aryl-α-oxysubstituted alkylcarboxylic acids is provided.

The compound of formula (IVg) where all other symbols are as defined earlier may be prepared by reacting a compound of formula (IVk)



(IVk)

where R^5 is hydrogen atom and all other symbols are as defined earlier, with an appropriate diazotizing agent.

The diazotization reaction may be under conventional conditions. A suitable diazotizing agent is an alkyl nitrile, such as iso-amyl nitrile. The reaction may be carried out in presence of solvents such as THF, dioxane, ether, benzene and the like or a combination thereof. Temperature in the range of –50°C to 80 may be used. The reaction may be carried out in an inert atmosphere which may be maintained by using inert gases such as N_2, Ar or He. The duration of the reaction may range from 1 to 24 h, preferably, 1 to 12 h.

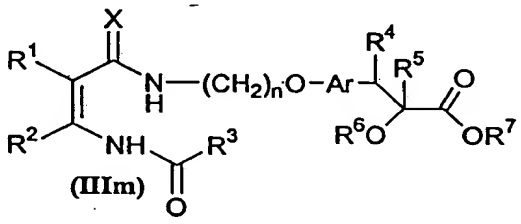
The compound of formula (IVk) may also be prepared by a reaction between (IIIh) where all symbols are as defined earlier and a compound of formula (IVl)

(IVl)

where R^5 is hydrogen atom and all other symbols are as defined earlier.

The reaction of compound of formula (IIIh) where all symbols are as defined earlier and a compound of formula (IVl) where all symbols are as defined earlier may be carried out in the presence of solvents such as THF, DMF, DMSO, DME and the like or mixtures thereof. The reaction may be carried out in an inert atmosphere which is maintained by using inert gases such as N_2, Ar or He. The reaction may be effected in the presence of a base such as K_2CO_3, Na_2CO_3 or NaH or mixtures thereof. Acetone may be used as a solvent when K_2CO_3 or Na_2CO_3 is used as a base. The reaction temperature may range from 20°C-120°C, preferably at a temperature in the range of 30°C-80°C. The duration of the reaction may range from 1 to 24 hours, preferably from 2 to 12 hours.

In another embodiment of the present invention there is provided the novel intermediate of formula (IIIm)



(IIIm)

where X represents O or S; the groups R^1, R^2 and R^3 when attached to the carbon atom may be same or different and represent hydrogen, halogen, hydroxy, nitro, cyano, formyl or unsubstituted or substituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, acyloxy, hydroxyalkyl, amino, acylamino, mono-alkylamino, dialkylamino, arylamino, aralkylamino, aminoalkyl, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkyl-thio, thioalkyl, alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino,

carboxylic acid or its derivatives, or sulfonic acid or its derivatives; R^1, R^2 along with the adjacent atoms to which they are attached may form a 5-6 membered substituted or unsubstituted cyclic structure containing carbon atoms with one or more double bonds, which may optionally contain one or more heteroatoms selected from oxygen, nitrogen and sulfur; R^3 when attached to nitrogen atom represents hydrogen, hydroxy, formyl or unsubstituted or substituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aralkyl, heterocyclyl, heteroaryl, heteroaralkyl, acyl, acyloxy, hydroxyalkyl, amino, acylamino, monoalkylamino, dialkylamino, arylamino, aralkylamino, aminoalkyl, aryloxy, aralkoxy, heteroaryloxy, heteroaralkoxy, alkoxy-carbonyl, aryloxycarbonyl, aralkoxy-carbonyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl groups, carboxylic acid derivatives, or sulfonic acid derivatives; the linking group represented by $-(CH_2)_n-O-$ may be attached either through nitrogen atom or through carbon atom where n is an integer ranging from 1 – 4; Ar represents an unsubstituted or substituted divalent single or fused aromatic or heterocyclic group; R^4 represents hydrogen atom, hydroxy, alkoxy, halogen, lower alkyl, unsubstituted or substituted aralkyl group or forms a bond together with the adjacent group R^5; R^5 represents hydrogen, hydroxy, alkoxy, halogen, lower alkyl group, acyl, unsubstituted or substituted aralkyl or R^5 forms a bond together with R^4; R^6 may be hydrogen, unsubstituted or substituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, alkoxyalkyl, alkoxycarbonyl, aryloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, acyl, heterocyclyl, heteroaryl, heteroaralkyl groups, with a provision that R^6 does not represent hydrogen when R^7 represents hydrogen or lower alkyl group; R^7 may be hydrogen or unsubstituted or substituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, or heteroaralkyl groups; Y represents oxygen or NR^8, where R^8 represents hydrogen, or unsubstituted or substituted alkyl, aryl, hydroxyalkyl, aralkyl, heterocyclyl, heteroaryl, or heteroaralkyl groups; R^7 and R^8 together may form a substitute or unsubstituted 5 or 6 membered cyclic structure containing carbon atoms, which may optionally contain one or more heteroatoms selected from oxygen, sulfur or nitrogen and a process for its preparation and its use in the preparation of β-aryl-α-oxysubstituted alkylcarboxylic acids is provided.

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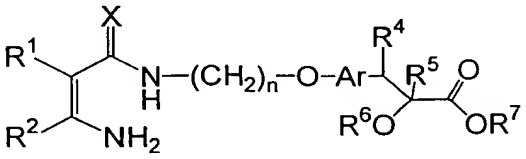
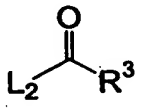
The compound of formula (IIIm) where all symbols are as defined earlier may be prepared by reacting a compound of fromula (IIIn)



(IIIn)

where all symbols are as defined earlier, with a compound of formula (IIIo)

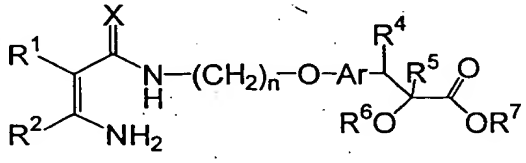


(IIIo)

where L^2 is halogen, -OH, $-OR^{10}$, or –O-C(=O)-OR^{10} where R^{10} is (C_1-C_5)alkyl and R^3 is as defined earlier.

The reaction of compound of formula (IIIn), where R^7 is as defined earlier excluding hydrogen and all other symbols are as defined above to produce a compound of general formula (IIIo) where all symbols are as defined above to produce a compound of general formula (IIIm), all symbols are as defined above may be carried out in neat or in the presence of solvents such as xylene, toluene, THF, dioxane, acetic acid, DMF, DMSO and the like of mixtures thereof. The reaction may be carried out in an inert atmosphere which may be maintained by using inert gases such as N_2, Ar or He. The reaction may be carried out at a temperature in the range of -10°C to 80°C, preferably at a temperature in the range of O°C to 60°C. The reaction may be effected in the presence or in absence of a base or an acid. The nature of the base or the acid is not critical. Bases such as pyridine, lutidine, triethyl amine, diisopropylethyl amine and the like and acids such as AcOH, C_2H_5COOH, butyric acid, trifluoroacetic acid, p-toluenesulfonic acid, benzenesulfonic acid and the like, may be used. The duration of the reaction may range from 0.25 to 24 hours, preferably from 0.50 to 6 hours.

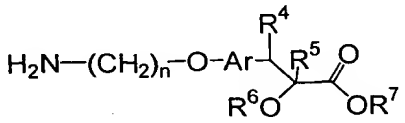
In yet another embodiment of the present invention there is provided the novel intermediates of formula (IIIn)



(IIIn)

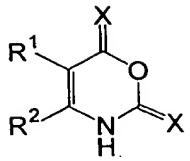
where X represents O or S; the groups R^1, R^2 may be same or different and represent hydrogen, halogen, hydroxy, nitro, cyano, formyl or unsubstituted or substituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, acyloxy, hydroxyalkyl, amino, acylamino, alkylamino, arylamino, aralkylamino, aminoalkyl, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, carboxylic acid or its derivatives, or sulfonic acid or its derivatives; or R^1, R^2 along with the adjacent atoms to which they are attached may also form a 5-6 membered substituted or unsubstituted cyclic structure containing carbon atoms with one or more double bonds, which may optionally contain one or more heteroatoms selected from oxygen, nitrogen and sulfur; n is an integer ranging from 1 – 4; Ar represents an unsubstituted or substituted divalent single or fused aromatic or heterocyclic group; R^4 represents hydrogen atom, hydroxy, alkoxy, halogen, lower alkyl, unsubstituted or substituted aralkyl group or forms a bond together with the adjacent group R^5; R^5 represents hydrogen, hydroxy, alkoxy, halogen, lower alkyl group, acyl, unsubstituted or substituted aralkyl or R^5 forms a bond together with R^4; R^6 may be hydrogen, or unsubstituted or substituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, alkoxyalkyl, alkoxycarbonyl, aryloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, acyl, heterocyclyl, heteroaryl, or heteroaralkyl groups, R^7 may be hydrogen or unsubstituted or substituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, heteroaralkyl groups and and a process for its preparation and its use in the preparation of β-aryl-α-oxysubstituted alkylcarboxylic acids is provided.

The compound of formula (IIIn) where all symbols are as defined above may be prepared by reacting a compound of formula (IVm)



(IVm)

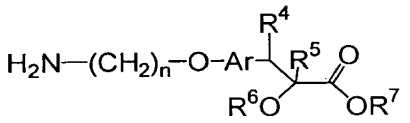
where all symbols are as defined earlier with a compound of formula (IVo)



(IVo)

The reaction of compound of formula (IVm) where all symbols are as defined earlier with a compound of formula (IVo) where R^1, R^2 and X are as defined earlier to produce a compound of formula (IIIm) defined earlier may be carried out neat or in the presence of solvents such as xylene, toluene, dioxane, THF, DMF, DMSO, DME and the like or their mixtures. The reaction may be carried out in an inert atmosphere which is maintained by using inert gases such as N_2, Ar or He. The reaction temperature may range from 0°C-150°C, preferably at a temperature in the range of 0°C-120°C. The duration of the reaction may range from 0.5 to 12 hours, preferably from 0.5 to 6 hours.

In still another embodiment of the present invention there is provided the novel intermediates of formula (IVm)



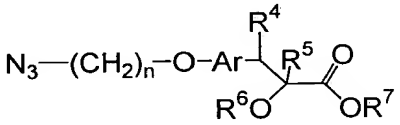
(IVm)

where n is an integer ranging from 1 – 4; Ar represents an unsubstituted or substituted divalent single or fused aromatic or heterocyclic group; R^4 represents hydrogen atom, hydroxy, alkoxy, halogen, lower alkyl, unsubstituted or substituted aralkyl group or forms a bond together with the adjacent group R^5; R^5 represents hydrogen, hydroxy, alkoxy, halogen, lower alkyl group, acyl, unsubstituted or substituted aralkyl or R^5 forms a bond together with R^4; R^6 may be hydrogen, or unsubstituted or substituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, alkoxyalkyl, alkoxycarbonyl, aryloxycarbonyl, alkylaminocarbonyl, arylamino-carbonyl, acyl, heterocyclyl, heteroaryl, heteroaralkyl groups; R^7 may be hydrogen or unsubstituted or substituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, hetero-cyclyl, heteroaryl, or heteroaralkyl groups.

The compound of general formula (IVm) where all symbols are as defined earlier may be prepared from a compound of formula (IIId) where all symbols are as

defined earlier by Gabriel synthesis. The reaction of phthalimide with the compound of formula (IIId) may be carried out neat or in presence of solvents such as ethanol, methanol, xylene, toluene, DMF, DME, dioxane and the like or mixtures thereof. The reaction may be carried out in presence of a base such as alkali metal carbonates like, K_2CO_3, Na_2CO_3 or alkali metal hydroxides like NaOH, KOH and the like or mixtures thereof. The reaction may be carried out in an inert atmosphere which is maintained by using inert gases such as N_2, Ar or He. The reaction temperature may range from 0°C-250°C, preferably at a temperature in the range of 15°C-200°C. The duration of the reaction may range from 0.1 to 48 hours, preferably from 1 to 12 hours. The hydrolysis of this intermediate may be carried under acidic conditions or using hydrazine.

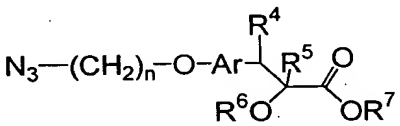
Alternatively, the compound of general formula (IVm) where R^4 and R^5 represent hydrogen atom and all other symbols are as defined earlier may be prepared by reducing a compound of formula (IVn)



(IVn)

where R^4 and R^5 together represent a bond and all other symbols are as defined earlier. The reduction may be carried out in the presence of gaseous hydrogen and a catalyst such as Pd/C, Rh/C, Pt/C, and the like. Mixtures of catalysts may be used. The reaction may also be conducted in the presence of solvents such as dioxane, acetic acid, ethyl acetate, alcohol such as methanol,ethanol and the like. A pressure between atmospheric pressure and 80 psi may be employed. The catalyst may be preferably 5-10%. Pd/C and the amount of catalyst used may range from 5-100% w/w. The reaction may also be carried out by employing metal solvent reduction such as magnesium in alcohol or sodium amalgam in alcohol, preferably methanol.

In still another embodiment of the present invention there is provided the novel intermediates of formula (IVn)



(IVn)

where n is an integer ranging from 1 – 4; Ar represents an unsubstituted or substituted divalent single or fused aromatic or heterocyclic group; R^4 represents hydrogen atom, hydroxy, alkoxy, halogen, lower alkyl, unsubstituted or substituted aralkyl group or forms a bond together with the adjacent group R^5; R^5 represents hydrogen, hydroxy, alkoxy, halogen, lower alkyl group, acyl, unsubstituted or substituted aralkyl or R^5 forms a bond together with R^4; R^6 may be hydrogen, or unsubstitured or substituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, alkoxyalkyl, alkoxycarbonyl, aryloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, acyl, heterocyclyl, hetero-aryl, or heteroaralkyl groups; R^7 may be hydrogen or unsubstituted or substituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, heteroaralkyl groups.

The compound of formula (IVn) may be prepared by treating a compound of general formula (IIId) where all symbols are as defined earlier with appropriate azides such as alkali metal azides like sodium azide, trialkylsilyl azide under conventional conditions. The reaction may be carried out neat or in the presence of solvents such as DMF, acetone, and the like or their mixtures. The reaction temperature may range from 0°C to 150°C, preferably at a temperature in the range of 25°C to 100°C. The duration of the reaction may be range from 0.5 to 48 h, preferably from 1 to 12 h.

Alternatively, the compound of general formula (IVn) where R^4 and R^5 represent a bond and all other symbols are as defined earlier may be prepared by reacting a compound of formula (IIIb) where R^6, R^7 are as defined earlier excluding hydrogen and R^9 represents (C_1-C_6)alkyl with a compound of formula (IVp)

$$N_3—(CH_2)_n—O—Ar—CHO \qquad \textbf{(IVp)}$$

where all symbols are as defined earlier, to yield a compound of general formula (IVn) where all symbols are as defined above may be carried out neat in the presence of a base such as alkali metal hydrides like NaH, KH or organolithiums like CH_3Li, BuLi and the like or alkoxides such as NaOMe, NaOEt, $BuO^- K^+$ or mixtures thereof. The reaction may be carried out in the presence of solvents such as THF, dioxane, DMF, DMSO, DME and the like or mixtures thereof. HMPA may be used as cosolvent. The reaction temperature may range from -78°C to 50°C, preferably at a temperature in the range of -10°C to 30°C. The reaction is more effective under anhydrous conditions.

The pharmaceutically acceptable salts are prepared by reacting the compound of formula (I) or a compound of formula (IIIm) whereever applicable with 1 to 4 equivalents of a base such as sodium hydroxide, sodium methoxide, sodium hydride, potassium t-butoxide, calcium hydroxide, magnesium hydroxide and the like, in solvents like ether, THF, methanol, t-butanol, dioxane, isopropanol, ethanol etc. Mixture of solvents may be used. Organic bases like lysine, arginine, diethanolamine, choline, tromethamine, guanidine and their derivatives etc. may also be used. Alternatively, acid addition salts wherever applicable are prepared by treatment with acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, p-toluenesulphonic acid, methanesulfonic acid, acetic acid, citric acid, maleic acid salicylic acid, hydroxynaphthoic acid, ascorbic acid, palmitic acid, succinic acid, benzoic acid, benzenesulfonic acid, tartaric acid and the like in solvents like ethyl acetate, ether, alcohols, acetone, THF, dioxane etc. Mixture of solvents may also be used.

The stereoisomers of the compounds forming part of this invention may be prepared by using reactants in their single enantiomeric form in the process wherever possible or by conducting the reaction in the presence of reagents or catalysts in their single enantiomer form or by resolving the mixture of stereoisomers by conventional methods. Some of the preferred methods include use of microbial resolution, resolving the diastereomeric salts formed with chiral acids such as mandelic acid, camphorsulfonic acid, tartaric acid, lactic acid, and the like wherever applicable or chiral bases such as brucine, cinchona alkaloids and their derivatives and the like. Commonly used methods are compiled by Jaques et al in "Enantiomers, Racemates and Resolution" (Wiley Interscience, 1981). More specifically the compound of formula (I) where YR^7 represents OH or a compound of formula (IIIm) may be converted to a 1:1 mixture of diastereomeric amides by treating with chiral amines, aminoacids, aminoalcohols derived from aminoacids; conventional reaction conditions may be employed to convert acid into an amide; the diastereomers may be separated either by fractional crystallization or chromatography and the stereoisomers of compound of formula (I) or a compound of formula (IIIm) may be prepared by hydrolyzing the pure diastereomeric amide.

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Various polymorphs of compound of general formula (I) and compounds of formula (IIIm) forming part of this invention may be prepared by crystallization of compound of formula (I) or compound of formula (IIIm) under different conditions. For example, using different solvents commonly used or their mixtures for crystallization; crystallizations at different temperatures; various modes of cooling, ranging from very fast to very slow cooling during crystallizations. Polymorphs may also be obtained by heating or melting the compound followed by gradual or fast cooling. The presence of poly-morphs may be determined by solid probe NMR spectroscopy, IR spectroscopy, differential scanning calorimetry, powder X-ray diffraction or such other techniques.

The compounds of general formula (I) or the compounds of formula (IIIm) are useful for the treatment and/or prophylaxis diseases such as hypertension, coronary heart disease, atherosclerosis, stroke, peripheral vascular diseases and related disorders. These compounds are useful for the treatment of familial hypercholesterolemia, hypertriglyceridemia, lowering of atherogenic lipoproteins, VLDL and LDL. The compounds of the present invention can be used for the treatment of certain renal diseases including glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis, retinopathy, and nephropathy. The compounds of general formula (I) or the compositions of formula (IIIm) are also useful for the treatment/prophylaxis of insulin resistance (type II diabetes), leptin resistance, impaired glucose tolerance, dyslipidemia, disorders related to syndrome X such as hypertension, obesity, insulin resistance, coronary heart disease, and other cardiovascular disorders. These compounds may also be useful as aldose reductase inhibitors, for improving cognitive functions in dementia, treating diabetic complications, disorders related to endothelial cell activation, psoriasis, polycystic ovarian syndrome (PCOS), inflammatory bowel diseases, osteoporosis, myotonic dystrophy, pancreatitis, arteriosclerosis, xanthoma and for the treatment of cancer. The compounds of the present inventions are useful in the treatment and/or prophylaxis of the above said diseases in combination/concomittant with one or more HMG CoA reductase inhibitors, hypolipidemic/hypolipoproteinemic agents such as fibric acid derivatives, nicotinic acid, cholestyramine, colestipol, or probucol. The compounds of the present invention in combination with HMG CoA reductase

inhibitors, and/or hypolipidemic/hypolipoproteinemic agents can be administered together or within such a period to act synergistically. The HMG CoA reductase inhibitors may be selected from those used for the treatment or prevention of hyperlipidemia such as lovastatin, provastatin, simvastatin, fluvastatin, atorvastatin, cerivastatin and their analogs thereof. Suitable fibric acid derivative may be gemfibrozil, clofibrate, fenofibrate, ciprofibrate, benzafibrate and their analogs thereof.

The present invention also provides a pharmaceutical composition, containing a compound of the general formula (I) or compounds of formula (IIIm), as defined above, their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates in combination with the usual pharmaceutically employed carriers, diluents and the like.

The pharmaceutical composition may be in the forms normally employed, such as tablets, capsules, powders, syrups, solutions, suspensions and the like, may contain flavourants, sweeteners etc. in suitable solid or liquid carriers or diluents, or in suitable sterile media to form injectable solutions or suspensions. Such compositions typically contain from 1 to 20%, preferably 1 to 10% by weight of active compound, the remainder of the composition being pharmaceutically acceptable carriers, excipients, diluents, solvents and the like.

The compounds of formula (I) or the compounds of formula (IIIm) as defined above are clinically administered to mammals, including man, via either oral or parenteral routes. Administration by the oral route is preferred, being more convenient and avoiding the possible pain and irritation of injection. However, in circumstances where the patient cannot swallow the medication, or absorption following oral administration is impaired, as by disease or other abnormality, it is essential that the drug be administered parenterally. By either route, the dosage is in the range of about 0.01 to about 100 mg/kg body weight of the subject per day or preferably about 0.01 to about 30 mg/kg body weight per day administered singly or as a divided dose. However, the optimum dosage for the individual subject being treated will be determined by the person responsible for treatment, generally smaller doses being administered initially and thereafter increments made to determine the most suitable dosage.

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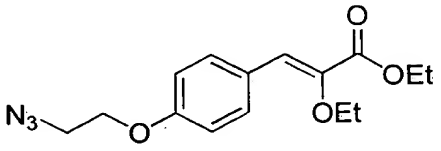
Suitable pharmaceutically acceptable carriers include solid fillers or diluents and sterile aqueous or organic solutions. The active compound will be present in such pharmaceutical compositions in the amounts sufficient to provide the desired dosage in the range as described above. Thus, for oral administration, the compounds can be combined with a suitable solid or liquid carrier or diluent to form capsules, tablets, powders, syrups, solutions, suspensions and the like. The pharmaceutical compositions, may, if desired, contain additional components such as flavourants, sweeteners, excipients and the like. For parenteral administration, the compounds can be combined with sterile aqueous or organic media to form injectable solutions or suspensions. For example, solutions in sesame or peanut oil, aqueous propylene glycol and the like can be used, as well as aqueous solutions of water-soluble pharmaceutically-acceptable acid addition salts or salts with base of the compounds. The injectable solutions prepared in this manner can then be administered intravenously, intraperitoneally, subcutaneously, or intramuscularly, with intramuscular administration being preferred in humans.

The invention is explained in detail in the examples given below which are provided by way of illustration only and therefore should not be construed to limit the scope of the invention.

Preparation 1

Ethyl 2-ethoxy-3-[4-(2-azidoethoxy)phenyl]-2-propenoate



Method A

To a stirred suspension of sodium hydride (390 mg, 9.83 mmol, 60%) in dry THF (20 mL) was added a solution of ethyl (diethylphosphono)ethoxyacetate (2.28 g, 8.52 mmol) in THF (10.0 mL) at 0-5°C dropwise and stirred for 30 min at 5-25°C. To the reaction mixture was added a solution of 4-(2-azidoethoxy)benzaldehyde (2.0 g, 6.56 mmol) in THF (5.0 mL) at 25-30°C and stirred further for 30 min. After completion of the reaction (tlc monitored), THF was removed and the resultant residue was diluted with water (50 mL) and extracted with ethyl acetate (3 X 25 mL). The

combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated to yield the title compound (3.0 g, 94%) as a mixture of E/Z isomers.

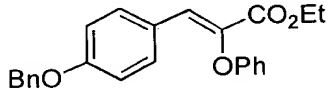
Method B

To a stirred solution of ethyl 2-ethoxy-3-[4-(2-bromoethoxy)phenyl]-2-propenoate (7.0 g, 20 mmol) prepared as disclosed in U.S. Patent Application Serial No. 09/012,585, sodium azide (2.0 g, 31 mmol) in dry DMF (40 mL) was added at *ca* 25°C and stirred for 16 h. Water was added and extracted with ethyl acetate (3 + 50 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated to yield the title compound as a colorless liquid (5.6 g, 92%).

^{1}H NMR ($CDCl_3$): δ 7.76 and 7.15 (d, J = 8.70 Hz, 2H), 7.02 – 6.75 (m, 2.6H), 6.08 (s, 0.4H), 4.35 – 3.80 (m, 6H), 3.72 – 3.61 (m, 2H), 1.48 – 1.20 (m, 6H).

Preparation 2

Ethyl 2-phenoxy-3-(4-benzyloxyphenyl)-2-propenoate

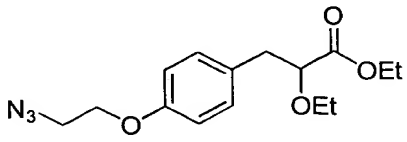


The title compound (1.66 g, 47%) as a mixture of *E/Z* isomers was obtained from 4-benzyloxybenzaldehyde (2.0 g, 9.4 mmol), ethyl (diethylphosphono) phenoxyacetate (3.0 g, 9.4 mmol) (*J. Org. Chem.* **1983**, *48*, 3407) and NaH (273 mg, 11.39 mmol, 95%) by a similar procedure to that described in preparation 1(method A).

^{1}H NMR ($CDCl_3$): δ 7.73 (d, J = 8.40 Hz, 1H), 7.60 - 7.25 (m, 9H), 7.18 - 6.92 (m, 5H), 5.12 and 5.08 (s, 2H), 4.22 and 4.15 (q, J = 7.05 Hz, 2H), 1.24 and 1.10 (t, J = 7.05 Hz, 3H).

Preparation 3

(±)-Ethyl 2-ethoxy-3-[4-(2-azidoethoxy)phenyl]propanoate

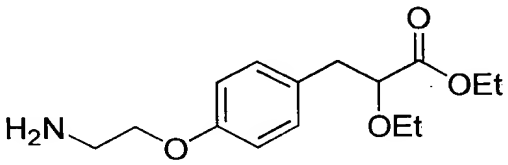


The title compound was obtained (16.8 g, 86%) from (±)-ethyl 2-ethoxy-3-[4-(2-bromoethoxy)phenylpropanoate (22.0 g, 63 mmol) prepared as disclosed in U.S. Patent Application Serial No. 09/012,585 and sodium azide (6.2 g, 95 mmol) by a similar procedure to that described in preparation 1(method B).

^{1}H NMR ($CDCl_3$): δ 7.17 (d, J = 8.63 Hz, 2H), 6.83 (d, J = 8.62 Hz, 2H), 4.25 – 4.05 (m, 4H), 3.96 (t, J = 6.57 Hz, 1H), 3.64 – 3.50 (m, 3H), 3.42 – 3.23 (m, 1H), 2.95 (d, J = 6.64 Hz, 2H), 1.30 – 1.09 (m, 6 H).

Preparation 4

(±)-Ethyl 2-ethoxy-3-[4-(2-aminoethoxy)phenyl]propanoate



Method A

A solution of (±)-ethyl 2-ethoxy-3-[4-(2-azidoethoxy)phenyl]propanoate (1.0 g, 3.25 mmol) obtained in preparation 3, in 1,4-dioxane (20 mL) was reduced with hydrogen in the presence of 10% palladium charcoal (100 mg) at 50 psi for 10 h. The reaction mixture was filtered through a bed of celite and the celite bed was washed with dioxane. The filtrate was evaporated to dryness under reduced pressure to yield the title compound (600 mg, 65%).

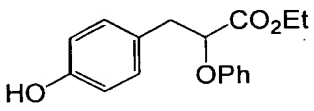
Method B

The title compound (450 mg, 49%) was obtained from ethyl 2-ethoxy-3-[4-(2-azidoethoxy)phenyl]2-propenoate (1.0 g, 3.27 mmol) obtained in preparation 1 and 10% Pd/C (500 mg) by a similar procedure to that described in method A above.

^{1}H NMR ($CDCl_3$): δ 7.15 (d, J = 7.82 Hz, 2H), 6.83 (d, J = 7.82 Hz, 2H), 4.10 (q, J = 7.02 Hz, 2H), 3.97 (t, J = 5.60 Hz, 2H), 3.70 – 3.50 (m, 1H), 3.50 – 3.25 (m, 1H), 3.40 – 2.95 (m, 2H), 3.07 (t, J = 4.77 Hz, 1H), 2.95 (d, J = 6.64 Hz, 2H), 0.95 (bs, 2H, D_2O exchangeable), 1.23 (t, J = 6.64 Hz, 3H), 1.17 (t, J = 7.05 Hz, 3H).

Preparation 5

(±)-Ethyl 2-phenoxy-3-(4-hydroxyphenyl)propanoate

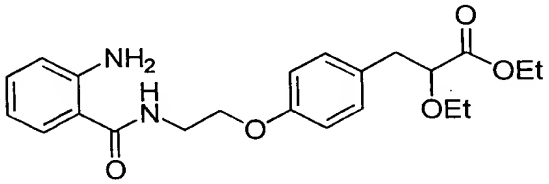


The title compound (1.03 g, 82%) was obtained from ethyl 2-phenoxy-3-(4-benzyloxyphenyl) -2-propenoate (1.65 g, 4.4 mmol) obtained in preparation 2 and 5% Pd-C (3.30 g) by a similar procedure to that described in preparation 4 (Method A).

^{1}H NMR ($CDCl_3$): δ 7.38 - 7.08 (m, 3H), 7.08 - 6.80 (m, 4H), 6.73 (d, J = 8.3 Hz, 2H), 4.73 (t, J = 6.43 Hz, 1H), 4.16 (q, J = 7.15 Hz, 2H), 3.16 (d, J = 6.40 Hz, 2H), 1.18 (t, J = 7.15 Hz, 3H).

Preparation 6

(±)-Ethyl 2-ethoxy-3-[4-[2-N-(2-aminobenzoyl)aminoethoxy]phenyl]propanoate

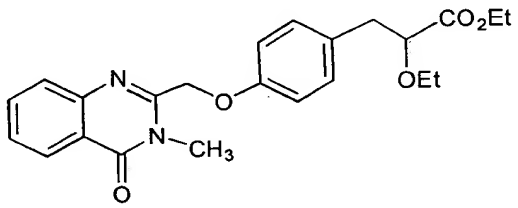


To a stirred solution of isatoic anhydride (1.57 g, 9.6 mmol) in 1,4-dioxane (30 mL) was added a solution of (±)-ethyl 2-ethoxy-3-[4-(2-aminoethoxy)phenyl] propanoate (3.0 g, 10.7 mmol) obtained in preparation 4 in 1,4-dioxane (10 mL) and stirred at room temperature for 2 h. Dioxane was removed under reduced pressure to yield the title compound as a brown coloured gummy liquid (3.8 g, 99%).

^{1}H NMR ($CDCl_3$): δ 7.34 (d, J = 7.91 Hz, 1H), 7.28 – 7.12 (m, 1H), 7.17 (d, J = 8.40 Hz, 2H), 6.83 (d, J = 8.40 Hz, 2H), 6.70 – 6.50 (m, 2H), 4.21 – 4.02 (m, 4H), 3.97 (t, J = 6.43 Hz, 1H), 3.81 (q, J = 5.07 Hz, 2H), 3.65 – 3.48 (m, 1H), 3.48 – 3.22 (m, 1H), 2.95 (d, J = 6.64 Hz, 2H), 1.23 (t, J = 7.06 Hz, 3H), 1.16 (t, J = 7.05 Hz, 3H).

Example 1

(±)-Ethyl 2-ethoxy-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl] methoxy] phenyl]propanoate



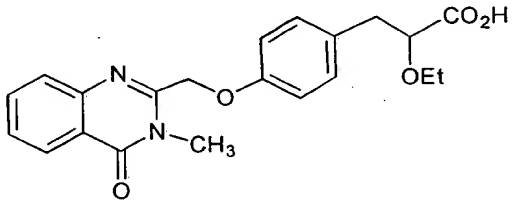
To a stirred solution of (±)-ethyl 2-ethoxy-3-(4-hydroxyphenyl)propanoate (7.6 g, 31.9 mmol) (disclosed in U.S. Patent Application Serial No. 09/012,585) potassium carbonate (8.81 g, 63.8 mmol) in dry DMF (60 mL) was added and stirred for 0.5 h at 30°C. To the reaction mixture was added 2-chloromethyl-3-methyl-4-oxo-3,4-dihydroquinazoline (10.0 g, 47.8 mmol) in one portion and stirred for 15 h at the same temperature. Water (100 mL) was added and extracted with ethyl acetate(3 + 100

mL). The combined ethylacetate extracts were washed with water, saturated sodium carbonate solution, brine, dried over anhydrous Na_2SO_4 and concentrated to yield the title compound (10.0 g, 70%). mp: 71–73°C.

^{1}H NMR ($CDCl_3$): δ 8.31 (d, J = 7.89 Hz, 1H), 7.84 - 7.65 (m, 2H), 7.52 (t, J = 7.90 Hz, 1H), 7.20 (d, J = 8.63 Hz, 2H), 6.98 (d, J = 8.63 Hz, 2H), 5.17 (s, 2H), 4.17 (q, J = 7.06 Hz, 2H), 3.97 (t, J = 6.41 Hz, 1H), 3.75 (s, 3H), 3.70 - 3.48 (m, 1H), 3.48 - 3.25 (m, 1H), 3.02 - 2.82 (m, 2H), 1.36 (m, 6H).

Example 2

(±)-2-Ethoxy-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl] propanoic acid

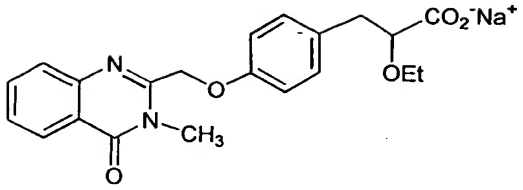


To a stirred solution of (±)-ethyl 2-ethoxy-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl]propanoate (10.0 g, 24.3 mmol) obtained in Example 1, in methanol (70 mL) was added a solution of sodium carbonate (12.93 g, 0.122 mmol) in water (70 mL) and stirred for 8 h at 25-30 °C. Methanol was removed under reduced pressure and the aqueous layer was washed with ethyl acetate (2 X 75 mL). The aqueous layer was acidified to pH 2.0 with 2N HCl. The white solid precipitated was filtered and dried to yield the title compound (8.0 g, 85.8%). mp: 80°C.

^{1}H NMR (DMSO-d_6): δ 8.29 (d, J = 7.89 Hz, 1H), 7.85 - 7.65 (m, 2H), 7.51 (t, J = 6.32 Hz, 1H), 7.19 (d, J = 8.63 Hz, 2H), 6.97 (d, J = 8.63 Hz, 2H), 5.16 (s, 2H), 4.04 (dd, J = 7.10 and 4.57 Hz, 1H), 3.34 (s, 3H), 3.72 - 3.50 (m, 1H), 3.50 - 3.35 (m, 1H), 3.15 - 2.85 (m, 2H), 1.16 (t, J = 7.94 Hz, 3H).

Example 3

(±)-Sodium 2-ethoxy-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy] phenyl]propanoate

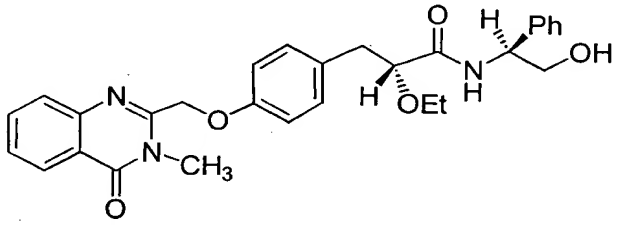


To a stirred suspension of (±)-2-ethoxy-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl]propanoic acid (4.0 g, 10.5 mmol), obtained in Example 2 in methanol (50 mL) was added a solution of sodium methoxide (2.27 g, 42 mmol) in methanol (10 mL) dropwise at 30°C. The reaction mixture was stirred for further 1 h. Diethyl ether (50 mL) was added and the white solid precipitated was filtered and dried to afford the title compound (3.2 g, 76%), mp: 210°C.

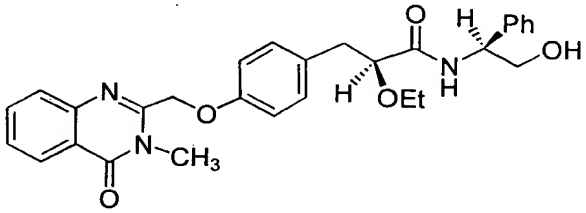
^{1}H NMR ($CDCl_3$): δ 8.17 (d, J = 7.06 Hz, 1H), 7.85 (t, J = 7.06 Hz, 1H), 7.69 (d, J = 7.88 Hz, 1H), 7.58 (t, J = 7.88 Hz, 1H), 7.17 (d, J = 8.62 Hz, 2H), 6.98 (d, J = 8.62 Hz, 2H), 5.24 (s, 2H), 3.68 (s, 3H), 3.60 - 3.48 (m, 1H), 3.25 - 3.00 (m, 1H), 2.85 (dd, J = 14.11 and 3.74 Hz, 1H), 2.62 (dd, J = 14.11 and 8.72 Hz, 1H), 2.60 - 2.48 (m, 1H), 0.97 (t, J = 7.06 Hz, 3H).

Example 4

[2R, N(1S)] 2-ethoxy-3-[4-[[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy] phenyl]-N-(2-hydroxy-1-phenylethyl)propanamide (4a)



[2S, N(1S)] 2-ethoxy-3-[4-[[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl] methoxy] phenyl]-N-(2-hydroxy-1-phenylethyl)propanamide (4b)



To a stirred solution of (±)-2-ethoxy-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl]propanoic acid (8.0 g, 20.9 mmol), obtained in Example

2, in dry dichloromethane (150 mL) was added triethylamine (7.28 mL, 5.29 g, 52.0 mmol) at 0°C, followed by addition of pivaloyl chloride (3.12 mL, 2.77 g, 23.0 mmol) and stirred for 30 min. at the same temperature. To this reaction mixture was added a solution of (S)-2-phenyl glycinol (2.87 g, 20.9 mmol) in dichloromethane (5 mL) containing triethylamine (5.8 mL, 41.8 mmol). After stirring for 1 h dichloromethane (600 mL) was added and the mixture was washed with water, brine, dried over anhydrous Na_2SO_4 and evaporated. The residue was chromatographed on silica gel using a gradient of 10-50% ethyl acetate in pet. ether as eluent to afford firstly a diastereomer tentatively assigned as [2R, N(1S)] 2-ethoxy-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl]-N-[2-hydroxy-1-phenylethyl]propanamide **(4a)** (4.5 g) followed by [2S, N(1S)] 2-ethoxy-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl]-N-[2-hydroxy-1-phenylethyl]propanamide **(4b)**.

Spectral data for **(4a)**:

$[\alpha]_D^{25}$ = + 41.60 (c = 0.5, MeOH), mp: 136-138°C.

^{1}H NMR ($CDCl_3$): δ 8.29 (d, J = 7.50 Hz, 1H), 7.82 - 7.62 (m, 2H), 7.51 (t, J = 7.50 Hz, 1H), 7.40 - 7.10 (m, 7H), 7.0 (d, J = 8.62 Hz, 2H), 5.18 (s, 2H), 5.00 - 4.88 (m, 1H), 3.98 (dd, J = 6.23 and 3.78 Hz, 1H), 3.75 (s, 3H), 3.70 - 3.55 (m, 2H), 3.50 (q, J = 7.01 Hz, 2H), 3.13 (dd, J = 14.12 and 3.78 Hz, 1H), 2.96 (dd, J = 14.12 and 6.23 Hz, 1H), 1.13 (t, J = 7.01 H, 3H).

Spectral data for **(4b)**:

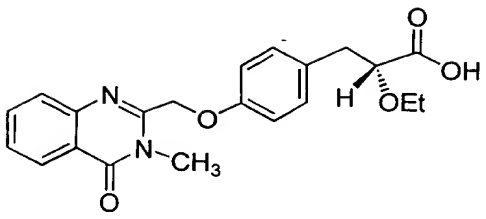
$[\alpha]_D^{25}$ = - 9.9 (c = 1.0, MeOH) mp: 126-128°C.

^{1}H NMR ($CDCl_3$): δ 8.30 (d, J = 8.89 Hz, 1H), 7.68 - 7.81 (m, 2H), 7.51 (t, J = 6.41 Hz,1H), 7.03 - 7.35 (m, 7H), 6.90 (d, J = 8.39 Hz, 2H), 5.13 (s, 2H), 4.91 - 5.01 (m, 1H), 3.99 (dd, J = 3.88 and 6.78 Hz, 1H), 3.85 (t, J = 5.35 Hz, 2H), 3.74 (s, 3H), 3.44 - 3.61 (m, 2H), 3.08 (dd, J = 3.88 and 14.12 Hz, 1H), 2.87 (dd, J = 6.78 and 14.12 Hz, 1H), 1.17 (t, J = 7.01 Hz, 3H).

<u>Example 5</u>

(+)-2-Ethoxy-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl] propanoic acid

09627005.071402



A solution of [2R, N(1S)] 2-ethoxy-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl] methoxy] phenyl]-N-[2-hydroxy-1-phenylethyl]propanamide (8.25 g, 16.50 mmol) obtained in Example 4a in a mixture of 1M sulphuric acid (212 mL) and dioxane/water (1 : 1, 1.7 L) was heated at 100°C for 16 h. The reaction mixture was cooled to *ca* 25°C and dioxane was removed under reduced pressure. The remaining solution was cooled in an ice bath and the white solid precipitated was filtered and dried to afford the title compound (3.6 g, 58%).

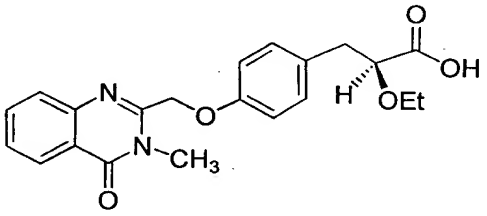
mp: 170°C.

$[\alpha]_D^{25}$ = 21.2 (c = 0.5, MeOH).

^{1}H NMR ($CDCl_3$): δ 8.29 (d, J = 7.88 Hz, 1H), 7.81 - 7.68 (m, 2H), 7.51 (t, J = 6.27 Hz, 1H), 7.19 (d, J = 8.62 Hz, 2H), 6.94 (d, J = 8.62 Hz, 2H), 5.16 (s, 2H), 4.04 (dd, J = 4.52 and 7.33 Hz, 1H), 3.70 (s, 3H), 3. 70 - 3.51 (m, 1H), 3.34 - 3.51 (m, 1H), 2.90 - 3.14 (m, 2H), 1.16 (t, J = 6.92 Hz, 3H).

Example 6

(-)-2-Ethoxy-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy] phenyl] propanoic acid



The title compound (3.0 g, 87%) was obtained from [2S, N(1S)] 2-ethoxy-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl]-N-[2-hydroxy-1-phenylethyl]propanamide (4.5 g, 8.9 mmol) obtained in example 4b, by a similar procedure to that described in Example 5.

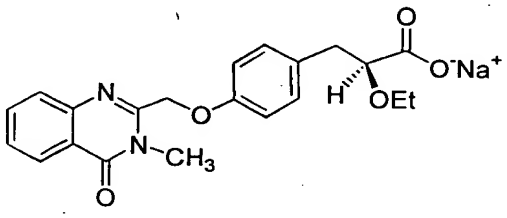
mp: 133-135°C.

$[\alpha]_D^{25}$ = - 20.84 (c = 1.0, MeOH).

^{1}H NMR ($CDCl_3$+DMSO-d_6): δ 8.22 (d, J = 7.56 Hz, 1H), 7.88 - 7.68 (m, 2H), 7.54 (t, J = 7.54 Hz, 1H), 7.20 (d, J = 8.62 Hz, 2H), 7.00 (d, J = 8.62 Hz, 2H), 5.24 (s, 2H), 3.93 (dd, J = 7.56 and 4.89 Hz, 1H), 3.71 (s, 3H), 3.70 - 3.50 (m, 1H), 3.42 - 3.22 (m, 1H), 3.05 - 2.78 (m, 2H), 1.12 (t, J = 7.06 Hz, 3H).

Example 7

(-)-Sodium 2-ethoxy-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy] phenyl]propanoate



The title compound (1.9 g, 85.5%) was obtained from (-)-2-ethoxy-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl]propanoic acid (2.1 g, 5.49 mmol) obtained in example 6 and 10% sodium methoxide solution (1.39 mL) by a similar procedure to that described in Example 3.

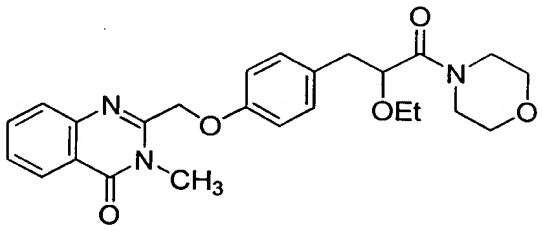
mp: 190°C.

$[\alpha]_D^{25}$ = -29.2 (c = 0.75 , MeOH).

^{1}H NMR (DMSO-d_6): δ 8.15 (d, J = 7.89 Hz, 1H), 7.83 (t, J = 7.47 Hz, 1H), 7.68 (d, J = 7.89 Hz, 1H), 7.56 (t, J = 7.31 Hz, 1H), 7.15 (d, J = 8.53 Hz, 2H), 6.96 (d, J = 8.63 Hz, 2H), 5.22 (s, 2H), 3.61 (s, 3H), 3.42 - 3.58 (m, 2H), 3.01 - 3.19 (m, 1H), 2.84 (dd, J = 3.64 and 14.12 Hz, 1H), 2.61 (dd, J = 9.04 and 14.12 Hz, 1H), 0.96 (t, J = 7.01 Hz, 3H).

Example 8

(±)-(Morpholine-4-yl) 2-ethoxy-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl] methoxy]phenyl]propanamide



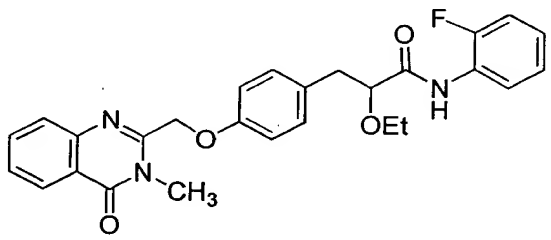
To a stirred solution of (±)-2-ethoxy-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl] methoxy]phenyl]propanoic acid (0.2 g, 0.52 mmol) obtained in Example 2 in dichloromethane (2 mL) was added triethylamine (182 µL, 0.13 g, 1.3 mmol) dropwise at 0°C. After stirring for 5 min was added pivaloyl chloride (78 µL, 69 mg, 0.57 mmol) and stirring continued for further 30 min at 0°C. To this reaction mixture was added a solution of morpholine (45 mL, 46 mg, 0.52 mmol) in dichloromethane containing triethylamine (145 µL, 1.0 mmol) at 25°C and stirred for 1 h at 25-30°C. To the reaction mixture chloroform (10 mL) was added and washed with water (2 + 10 mL), brine, dried over anhydrous Na_2SO_4 and concentrated. The crude compound was purified by column chromatography using ethyl acetate and pet. ether (1:1) as eluent to afford the title compound (184 mg, 78%).

mp: 115°C.

^{1}H NMR ($CDCl_3$): δ 8.26 (d, J = 7.57 Hz, 1H), 7.80 - 7.65 (m, 2H), 7.51 (t, J = 4.05 Hz, 1H), 7.15 (d, J = 8.58 Hz, 2H), 6.95 (d, J = 8.58 Hz, 2H), 5.14 (s, 2H), 4.24 (t, J = 6.75 Hz, 1H), 3.71 (s, 3H), 3.61 - 3.31 (m, 10 H), 2.95 (d, J = 6.75 Hz, 2H), 1.13 (t, J = 7.01 Hz, 3H).

Example 9

(±)-2-Ethoxy-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl]-N-(2-fluorophenyl)propanamide



The title compound (110 mg, 44%) was obtained from (±)-2-ethoxy-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl]propanoic acid (200 mg, 0.52 mmol) obtained in Example 2 and 2-fluoroaniline (50 µL, 58 mg, 0.52 mmol) by a similar procedure to that described in Example 8.

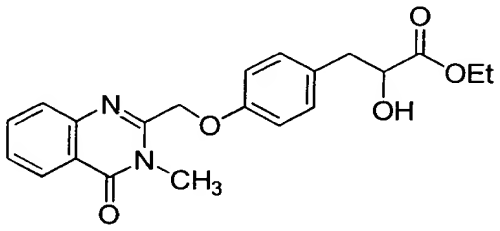
mp: 138-140°C.

^{1}H NMR ($CDCl_3$): δ 8.33 (t, J = 7.42 Hz, 2H), 7.83 - 7.69 (m, 2H), 7.52 (t, J = 6.43 Hz, 1H), 7.29 - 6.92 (m, 7H), 5.16 (s, 2H), 4.02 (dd, J = 7.89 and 3.4 Hz, 1H),

3.74 (s, 3H), 3.65 - 3.40 (m, 2H), 3.18 (dd, J = 14.11 and 3.41 Hz, 1H), 2.94 (dd, J = 14.11 and 7.89 Hz, 1H), 1.20 (t, J = 7.01 Hz, 3H).

Example 10

(±)-Ethyl 2-hydroxy-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy] phenyl]propanoate



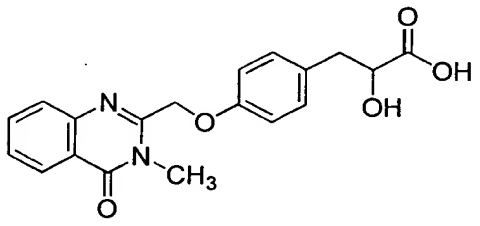
The title compound (6.5 g, 71%) was obtained from (±)-ethyl 2-hydroxy-3-(4-hydroxyphenyl) propanoate (5.0 g, 23.8 mmol) (DE 26 625 163), 2-chloromethyl-3-methyl-4-oxo-3,4-dihydro-quinazoline (5.0 g, 23.8 mmol) and potassium carbonate (6.57 g, 47.6 mmol) as a base by a similar procedure to that described in Example 1.

mp: 112-118°C.

^{1}H NMR ($CDCl_3$): δ 8.30 (d, J = 7.47 Hz,1H), 7.77 - 7.72 (m, 2H), 7.53 (t, J = 3.51 Hz, 1H), 7.18 (d, J = 8.57 Hz, 2H), 6.98 (d, J = 8.57 Hz, 2H), 5.16 (s, 2H), 4.41 (m, 1H), 4.23 (q, J = 7.10 Hz, 2H), 3.73 (s, 3H), 2.93 - 3.05 (m, 2H), 1.27 (t, J = 7.10 Hz, 3H).

Example 11

(±)-2-Hydroxy-3-[4-[[3-methyl-4-oxo-3, 4-dihydro-2-quinazolinyl] methoxy] phenyl]propanoic acid



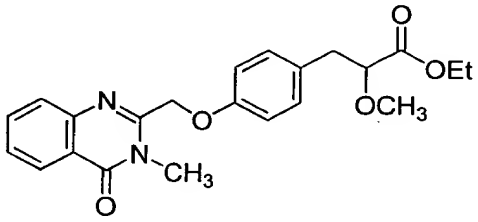
The title compound (0.5 g, 70.7%) was obtained from (±)-ethyl 2-hydroxy-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl]propanoate (764 mg, 2.0 mmol) obtained in Example 10 and sodium carbonate (1.06 g, 10.0 mmol) by a similar procedure to that described in Example 2.

mp: 184-188°C.

^{1}H NMR ($CDCl_3$+DMSO): δ 8.29 (d, J = 7.89 Hz, 1H), 7.77 - 7.73 (m, 2H), 7.53 (t, J = 4.06 Hz, 1H), 7.23 (d, J = 8.39 Hz, 2H), 6.98 (d, J = 8.39 Hz, 2H), 5.15 (s, 2H), 4.37 (dd, J = 6.99 Hz and 4.08 Hz, 1H), 3.73 (s, 3H), 3.05 (dd, J = 14.03 Hz, 4.0 Hz, 1H), 2.90 (dd, J = 14.03 Hz, and 6.99 Hz, 1H).

Example 12

(±)-Ethyl 2-methoxy-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl] methoxy] phenyl]propanoate

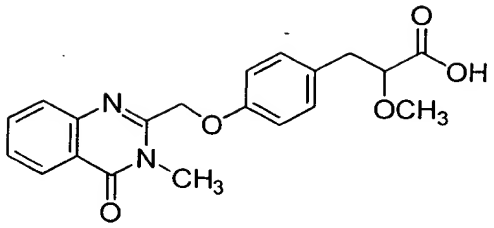


To a stirred suspension of sodium hydride (270 mg, 10.46 mmol, 95%) in dry DMF (2 mL) was added a solution of (±)-ethyl 2-hydroxy-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy] phenyl]propanoate (2.0 g, 5.23 mmol) obtained in example 10 at 0°C and stirred for 30 min. To the reaction mixture was added methyl iodide (1.62 mL, 26.15 mmol) at the same temperature and stirring continued for further 1h. After completion of the reaction, diluted with ethyl acetate (150 mL), washed with brine (3 x 100 mL), dried over anhydrous Na_2SO_4 and concentrated. The crude compound was purified by column chromatography using ethyl acetate and pet. Ether (1:9) as eluent to afford the title compound as a liquid (480 mg, 23%).

^{1}H NMR ($CDCl_3$): δ 8.28 (d, J = 8.89 Hz, 1H), 7.70 - 7.68 (m, 2H), 7.53 (t, J = 4.06 Hz, 1H), 7.19 (d, J = 8.40 Hz, 2H), 6.97 (d, J = 8.63 Hz, 2H), 5.15 (s, 2H), 4.18 (q, J = 7.10 Hz, 2H), 3.98 (dd, J = 4.56 and 7.06 Hz, 1H), 3.73 (s, 3H), 3.39 (s, 3H), 3.12 - 2.99 (m, 2H), 1.25 (t, J = 7.10 Hz, 3H).

Example 13

(±)-2-Methoxy-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl] propanoic acid



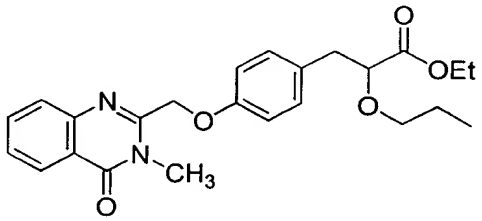
The title compound (355 mg, 80%) was obtained from (±)-ethyl 2-methoxy-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl]propanoate (480 mg, 1.21 mmol) obtained in example 12 and sodium carbonate (640 mg, 6.06 mmol) by a similar procedure to that described in Example 2.

mp: 99-101°C.

^{1}H NMR ($CDCl_3$): δ 8.29 (d, J = 7.89 Hz, 2H), 7.82 - 7.68 (m, 2H), 7.55 (t, J = 7.89 Hz, 1H), 7.19 (d, J = 8.62 Hz, 2H), 6.97 (d, J = 8.62 Hz, 2H), 5.15 (s, 2H), 3.98 (dd, J = 7.06 and 4.56 Hz, 1H), 3.74 (s, 3H), 3.39 (s, 3H), 3.18 - 2.82 (m, 2H).

Example 14

(±)-Ethyl 2-propoxy-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy] phenyl]propanoate



The title compound (1.23 g, 55%) was obtained as a liquid from (±)-ethyl 2-hydroxy-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl] methoxy] phenyl] propanoate (2.0 g, 5.23 mmol) obtained in Example 10, propylbromide (2.5 ml, 23.17 mmol) and sodium hydride (270 mg, 10.46 mmol) as a base by a similar procedure to that described in Example 12.

^{1}H NMR ($CDCl_3$): δ 8.29 (d, J = 8.12 Hz, 1H), 7.80 - 7.65 (m, 2H), 7.50 (t, J = 7.50 Hz, 1H), 7.18 (d, J = 8.40 Hz, 2H), 6.96 (d, J = 8.30 Hz, 2H), 5.15 (s, 2H), 4.16 (q, J = 7.35 Hz, 2H), 3.95 (t, J = 6.32 Hz, 1H), 3.74 (s, 3H), 3.53 - 3.49 (m, 1H), 3.22 - 3.18 (m, 1H), 2.96 (d, J = 6.32 Hz, 2H), 1.70 - 1.40 (m, 2H), 1.20 (t, J = 7.25 Hz, 3H), 0.82 (t, J = 7.35 Hz, 3H).

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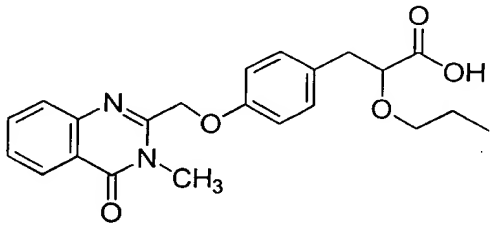
Example 15

(±)-2-Propoxy-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy] phenyl]propanoic acid



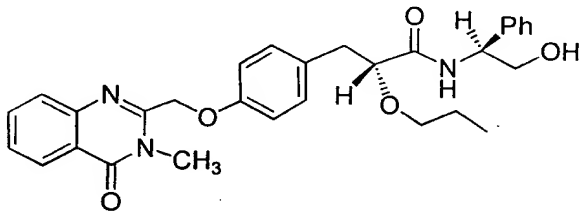
The title compound (310 mg, 81%) was obtained from (±)-ethyl 2-propoxy-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl]propanoate (410 mg, 0.97 mmol) obtained in Example 14 and sodium carbonate (512 mg, 4.83 mmol) by a similar procedure to that described in Example 2.

mp: 167-168°C.

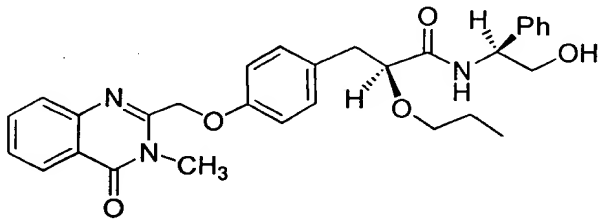
^{1}H NMR ($CDCl_3$): δ 8.29 (d, J = 7.88 Hz, 1H), 7.82 - 7.63 (m, 2H), 7.53 (t, J = 7.88 Hz, 1H), 7.19 (d, J = 8.62 Hz, 2H), 6.97 (d, J = 8.62 Hz, 2H), 5.16 (s, 2H), 4.05 (dd, J = 7.28 and 4.25 Hz, 1H), 3.74 (s, 3H), 3.60 - 3.40 (m, 1H), 3.40 - 3.25 (m, 1H), 3.20 - 2.90 (m, 2H), 1.56 (s, J = 7.05 Hz, 2H), 0.85 (t, J = 7.43 Hz, 3H).

Example 16

[2S, N(1S)] 2-propoxy-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl] methoxy]phenyl]-N-(2-hydroxy-1-phenylethyl)propanamide (16a)



[2R, N(1S)] 2-Propoxy-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl] methoxy]phenyl]-N-(2-hydroxy-1-phenylethyl)propanamide (16b)



The title compounds [2S, N(1S)] propanamide **(16a)** and [2R, N(1S)] propanamide **(16b)** were obtained from (±)-2-propoxy-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy] phenyl]propanoic acid (30 mg, 0.075 mmol) obtained in Example 15, triethylamine (47 µL, 0.33 mmol), pivaloyl chloride (11 µL, 0.083 mmol) and S-(+)-2-phenyl glycinol (10 mg, 0.075 mmol) by a similar procedure to that described in Example 4.

Spectral data for **(16a)**:

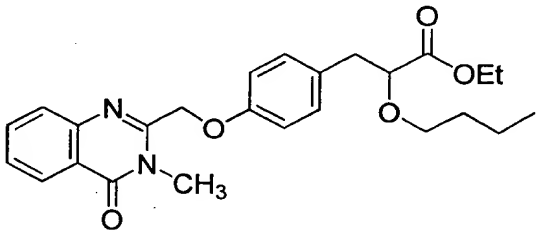
^{1}H NMR ($CDCl_3$): δ 8.31 (d, J = 8.31 Hz, 1H), 7.69 - 7.82 (m, 2H), 7.50 - 7.60 (m, 1H), 7.12 - 7.39 (m, 7H), 6.94 (d, J = 6.23 Hz, 2H), 5.19 (s, 2H), 4.89 - 5.01 (m, 1H), 3.98 (dd, J = 3.73 and 5.90 Hz, 1H), 3.76 (s, 3H), 3.60 - 3.67 (m, 2H), 3.38 (q, J = 2.89 Hz, 2H), 3.13 (dd, J = 3.73 and 14.12 Hz, 1H), 2.95 (dd, J = 5.90 and 14.12 Hz, 1H), 1.54 (q, J = 7.16 Hz, 2H), 0.84 (t, J = 7.40 Hz, 3H).

Spectral Data for **(16b)**:

^{1}H NMR ($CDCl_3$): δ 8.32 (d, J = 7.89 Hz, 1H), 7.86 - 7.70 (m, 2H), 7.58 - 7.49 (m, 1H), 7.39 - 7.08 (m, 7H), 6.92 (d, J = 8.40 Hz, 2H), 5.15 (s, 2H), 5.08 - 4.91 (m, 1H), 4.00 (dd, J = 3.73 and 6.73 Hz, 1H), 3.87 (d, J = 4.89 Hz, 2H), 3.76 (s, 3H), 3.44 (q, J = 3.46 Hz, 2H), 3.10 (dd, J = 3.73 and 14.11 Hz, 1H), 2.90 (dd, J = 6.73 and 14.11 Hz, 1H), 1.58 (q, J = 6.95 Hz, 2H), 0.90 (t, J = 7.42 Hz, 3H).

Example 17

(±)-Ethyl 2-(n-butoxy)-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl] methoxy]phenyl]propanoate

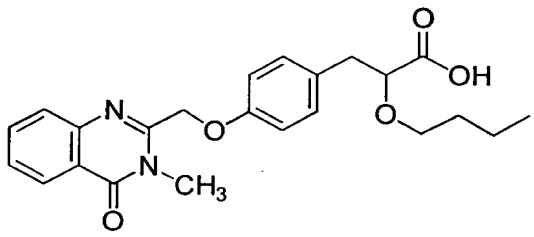


The title compound (270 mg, 47%) was obtained as a liquid from (±)-ethyl 2-hydroxy-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl] methoxy] phenyl] propanoate (500 mg, 1.31 mmol) obtained in Example 10, butyl bromide (0.7 mL, 0.64 mmol) and sodium hydride (50 mg, 1.96 mmol) as a base by a similar procedure to that described in Example 12.

^{1}H NMR ($CDCl_3$): δ 8.30 (d, J = 7.47 Hz, 1H), 7.81 - 7.65 (m, 2H), 7.58 - 7.43 (m, 1H), 7.18 (d, J = 8.62 Hz, 2H), 6.96 (d, J = 8.62 Hz, 2H), 5.16 (s, 2H), 4.15 (q, J = 7.15 Hz, 2H), 3.93 (t, J = 6.40 Hz, 1H), 3.74 (s, 3H), 3.60 - 3.45 (m, 1H), 3.30 - 3.15 (m, 1H), 2.95 (d, J = 6.40 Hz, 2H), 1.78 - 1.40 (m, 4H), 1.21 (t, J = 7.15 Hz, 3H), 0.83 (t, J = 7.35 Hz, 3H).

Example 18

(±)-2-(n-Butoxy)-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy] phenyl]propanoic acid



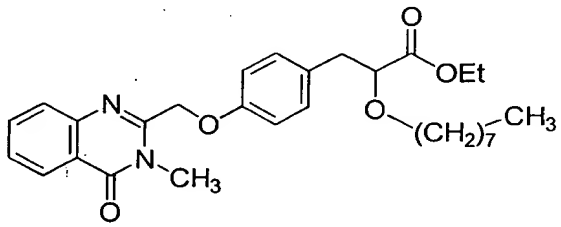
The title compound (320 mg, 80%) was obtained from (±)-ethyl 2-(n-butoxy)-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl]propanoate (430 mg, 0.98 mmol), obtained in Example 17 and sodium carbonate (520 mg, 4.91 mmol) by a similar procedure to that described in Example 2.

mp: 145°C.

^{1}H NMR ($CDCl_3$): δ 8.30 (d, J = 7.85 Hz, 1H), 7.85 - 7.60 (m, 2H), 7.54 (t, J = 7.85 Hz, 1H), 7.20 (d, J = 8.62 Hz, 2H), 6.98 (d, J = 8.62 Hz, 2H), 5.17 (s, 2H), 4.05 (dd, J = 7.28 and 4.25 Hz, 1H), 3.74 (s, 3H), 3.65 - 3.48 (m, 1H), 3.28 - 3.32 (m, 1H), 3.20 - 2.86 (m, 2H), 1.65 - 1.40 (m, 2H), 1.40 - 1.20 (m, 2H), 0.87 (t, J = 7.15 Hz, 3H).

Example 19

(±)-Ethyl 2-(n-octyloxy)-3-[4-[[3-methyl-4-oxo-3,4-dihydro 2-quinazolinyl] methoxy]phenyl] propanoate



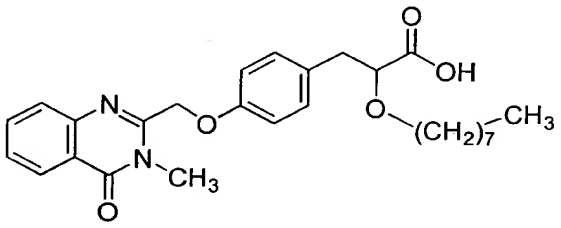
The title compound (240 mg, 38%) was obtained as a liquid from (±)-ethyl 2-hydroxy-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy] phenyl]

propanoate (500 mg, 1.31 mmol) obtained in Example 10, n-octylbromide (1.1 mL, 6.54 mmol) and sodium hydride (50 mg, 1.96 mmol, 95%) as a base by a similar procedure to that described in Example 12.

^{1}H NMR ($CDCl_3$): δ 8.30 (d, J = 8.3 Hz, 1H), 7.85 - 7.65 (m, 2H), 7.51 (t, J = 8.02 Hz, 1H), 7.19 (d, J = 8.62 Hz, 2H), 6.96 (d, J = 8.62 Hz, 2H), 5.15 (s, 2H), 4.16 (q, J = 7.15 Hz, 2H), 3.94 (t, J = 6.52 Hz, 1H), 3.74 (s, 3H), 3.60 - 3.48 (m, 1H), 3.31 - 3.18 (m, 1H), 2.95 (d, J = 6.32 Hz, 2H), 1.80 - 1.40 (m, 4H), 1.40 - 1.05 (m, 11 H), 0.87 (t, J = 6.67 Hz, 3H).

Example 20

(±) 2-(n-Octyloxy)-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl] methoxy] phenyl]propanoic acid



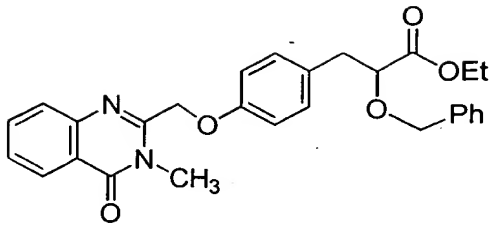
The title compound (350 mg, 88%) was obtained from (±)-ethyl 2-(n-octyloxy) -3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy] phenyl]propanoate (437 mg, 0.88 mmol) obtained in Example 19 and sodium carbonate (468 mg, 4.40 mmol) by a similar procedure to that described in Example 2.

mp: 99-100°C.

^{1}H NMR ($CDCl_3$): δ 8.31 (d, J = 8.3 Hz, 1H), 7.82 - 7.65 (m, 2H), 7.51 (t, J = 8.02 Hz, 1H), 7.19 (d, J = 8.62 Hz, 2H), 6.97 (d, J = 8.62 Hz, 2H), 5.16 (s, 2H), 4.10 - 4.00 (m, 1H), 3.74 (s, 3H), 3.62 - 3.45 (m, 1H), 3.45 - 3.28 (m, 1H), 3.18 - 2.88 (m, 2H), 1.68 - 1.42 (m, 2H), 1.42 - 1.12 (m, 10 H), 0.88 (t, J = 5.88 Hz, 3H).

Example 21

(±)-Ethyl 2-benzyloxy-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl] methoxy]phenyl] propanoate

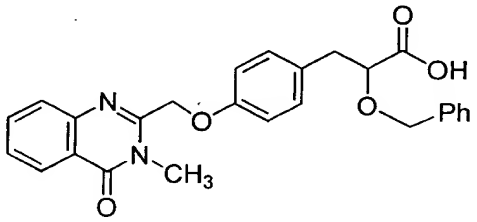


The title compound (1.40 g, 57%) was obtained as a liquid from (±)-ethyl 2-hydroxy-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy] phenyl] propanoate (2.0 g, 5.23 mmol) obtained in Example 10, benzyl bromide (1.07 g, 6.28 mmol) and sodium hydride (260 mg, 10.46 mmol, 95%) by a similar procedure to that described in Example 12.

^{1}H NMR ($CDCl_3$): δ 8.30 (d, J = 7.89 Hz, 1H), 7.76 - 7.63 (m, 2H), 7.54 (t, J = 7.89 Hz, 1H), 7.46 - 7.04 (m, 5H),7.20 (d, J = 8.72 Hz, 2H), 6.96 (d, J = 6.89 Hz, 2H), 5.16 (s, 2H), 4.66 (d, J = 11.85 Hz, 1H), 4.36 (d, J = 11.85 Hz, 1H), 4.30 - 4.00 (m, 3H), 3.74 (s, 3H), 3.08 - 2.92 (m, 2H), 1.24 (q, J = 7.15 Hz, 3H).

Example 22

(±)-2-Benzyloxy-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl] methoxy] phenyl]propanoic acid



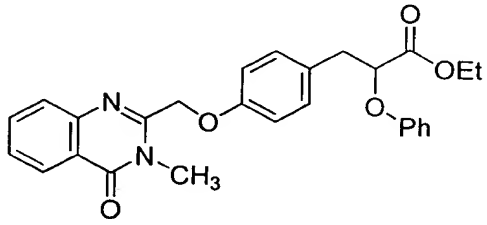
The title compound (1.0 g, 77%) was obtained from (±)-ethyl 2-benzyloxy-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl]propanoate (1.40 g, 2.97 mmol) obtained in Example 21 and sodium carbonate (1.57 g, 14.81 mmol) by a similar procedure to that described in Example 2.

mp: 152-154°C.

^{1}H NMR ($CDCl_3$): δ 8.30 (d, J = 7.89 Hz, 1H), 7.82 - 7.68 (m, 2H), 7.53 (t, J = 7.89 Hz, 1H), 7.35 - 7.18 (m, 5H), 7.19 (d, J = 8.72 Hz, 2H), 6.97 (d, J = 8.72 Hz, 2H), 5.16 (s, 2H), 4.64 (d, J = 11.62 Hz, 1H), 4.43 (d, J = 11.2 Hz, 1H), 4.16 (dd, J = 7.45 and 4.55 Hz, 1H), 3.74 (s, 3H), 3.20 - 2.91 (m, 2H).

Example 23

(±)-Ethyl 2-phenoxy 3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl] methoxy] phenyl]propanoate

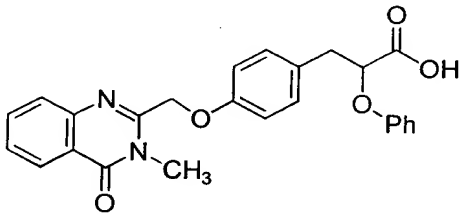


The title compound (900 mg, 95%) was obtained as a liquid from (±)-ethyl 2-phenoxy-3-(4-hydroxyphenyl)propanoate (660 mg, 2.3 mmol) obtained in preparation 5 , 2-chloromethyl-3-methyl-4-oxo-3,4-dihydroquinazoline (563 mg, 2.7 mmol) and potassium carbonate (637 mg, 4.61 mmol) as a base by a similar procedure described in Example 1.

^{1}H NMR ($CDCl_3$): δ 8.29 (d, J = 7.89 Hz, 1H), 7.65 - 7.80 (m, 2H), 7.50 (t, J = 7.10 Hz, 1H), 7.15 - 7.32 (m, 5H), 6.92 - 7.05 (m, 2H), 6.84 (d, J = 7.98 Hz, 2H), 5.16 (s, 2H), 4.75 (t, J = 6.39 Hz, 1H), 4.16 (q, J = 6.36 Hz, 2H), 3.72 (s, 3H), 3.20 (d, J = 6.64 Hz, 2H), 1.17 (t, J = 7.15 Hz, 3H).

Example 24

(±)-2-Phenoxy-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl] propanoic acid



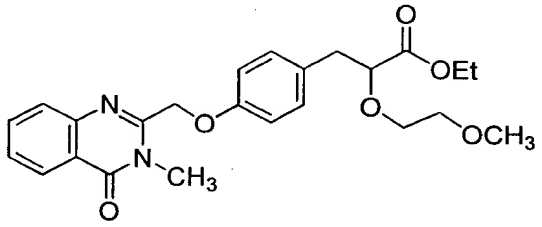
The title compound (0.45 g, 53%) was obtained from (±)-ethyl 2-phenoxy-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl]propanoate (900 mg, 1.96 mmol) obtained in Example 23 and sodium carbonate (1.04 g, 9.82 mmol) by a similar procedure to that described in Example 2.

mp: 156-158°C.

^{1}H NMR ($CDCl_3$): δ 8.31 (d, J = 7.89 Hz, 1H), 7.85 - 7.65 (m, 2H), 7.52 (t, J = 6.39 Hz, 1H), 7.35 - 7.21 (m, 5H), 7.02 - 6.96 (m, 2H), 6.87 (d, J = 7.93 Hz, 2H), 5.15 (s, 2H), 4.85 (t, J = 6.02 Hz, 1H), 3.73 (s, 3H), 3.26 (d, J = 6.14 Hz, 2H).

Example 25

(±)-Ethyl 2-(2-methoxyethoxy)-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl] methoxy]phenyl]propanoate

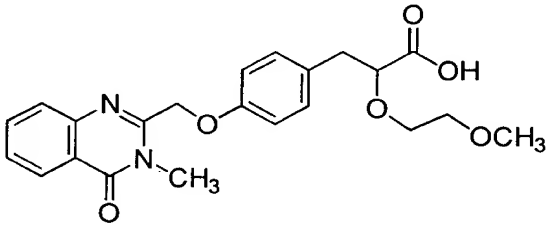


The title compound (560 mg, 83%) was obtained from (±)-ethyl 2-(2-methoxy-ethoxy)-3-(4-hydroxyphenyl)propanoate (410 mg, 1.529 mmol), 2-chloromethyl-3-methyl-4-oxo-3,4-dihydroquinazoline (640 mg, 3.058 mmol) and potassium carbonate (634 mg, 4.58 mmol) as a base by a similar procedure to that described in Example 1.

^{1}H NMR ($CDCl_3$): δ 8.31 (d, J = 7.45 Hz, 1H), 7.84 - 7.68 (m, 2H), 7.51 (t, J = 6.41 Hz, 1H), 7.20 (d, J = 8.61 Hz, 2H), 6.98 (d, J = 8.61 Hz, 2H), 5.18 (s, 2H), 4.21 - 4.02 (m, 4H), 3.76 (s, 3H), 3.75 - 3.66 (m, 1H), 3.65 - 3.40 (m, 3H), 3.31 (s, 3H), 3.01 - 2.96 (m, 1H), 1.22 (t, J = 7.15 Hz, 3H).

Example 26

(±)-2-(2-Methoxyethoxy)-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl] methoxy]phenyl]propanoic acid



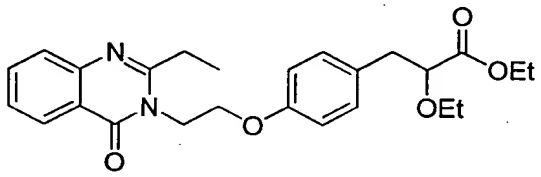
The title compound (270 mg, 51%) was obtained from (±)-ethyl 2-(2-methoxy-ethoxy)-3-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl] methoxy] phenyl] propanoate (560 mg, 1.27 mmol) obtained in Example 25 and sodium carbonate (675 mg, 6.36 mmol) by a similar procedure to that described in Example 2.

mp: 146-148°C.

^{1}H NMR ($CDCl_3$): δ 8.30 (d, J = 7.47 Hz, 1H), 7.82 - 7.69 (m, 2H), 7.52 (t, J = 6.41 Hz, 1H), 7.21 (d, J = 8.63 Hz, 2H), 6.99 (d, J = 8.63 Hz, 2H), 5.17 (s, 2H), 4.06 (dd, J = 3.46 and 8.76 Hz, 1H), 3.75 (s, 3H), 3.71 - 3.42 (m, 4H), 3.40 (s, 3H), 3.19 (dd, J = 3.46 and 14.16 Hz, 1H), 2.91 (dd, J = 8.76 and 14.16 Hz, 1H).

Example 27

(±)-Ethyl 2-ethoxy-3-[4-[2-[2-ethyl-4-oxo-3,4-dihydro-3-quinazolinyl]ethoxy] phenyl]propanoate



Method A

To a stirred solution of 2-ethyl-4-oxo-3,4-dihydroquinazoline (200 mg, 1.15 mmol) in DMF (3 mL) was added potassium carbonate (317 mg, 2.30 mmol) and stirred for 30 min. To this reaction mixture was added a solution of (±) ethyl 2-ethoxy -3-[4-(2-bromoethoxy)phenyl]propanoate (475 mg, 1.38 mmol) (disclosed in U.S. Patent Application Serial No. 09/012,585) in DMF (2 mL) and stirred for 24 h at 30°C. The reaction mixture was diluted with water and extracted with ethyl acetate (3 + 10 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated to yield the title compound (260 mg, 51%).

Method B

To a stirred suspension of sodium hydride (1.15 g, 28.7 mmol, 60%) in dry DMF (60 mL) was added 2-ethyl-4-oxo-3,4-dihydroquinazoline (5.0 g, 28.7 mmol) at 0°C and stirred for 0.5 h at the same temperature. To the reaction mixture was added lithium bromide (5.0 g, 57.47 mmol) in one portion and stirring continued for further 0.5 h at 0°C. A solution of (±) ethyl 2-ethoxy-3-[4-(2-bromoethoxy) phenyl] propanoate (14.87 g, 43.1 mmol), in dry DMF (20 mL) was added and stirred for 5 h at 30°C. The reaction mixture was diluted with water and extracted with ethyl acetate (3 + 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated to yield the title compound (6.1 g, 48%).

Method C

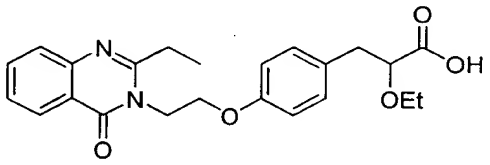
To a stirred solution of (±) ethyl 2-ethoxy-3-[4-[2-[N-(2-aminobenzoyl) amino-ethoxy]phenyl] propanoate (15 g, 37.5 mmol) obtained in preparation 6, in a mixture of xylene (50 mL) and propionic acid (50 mL) was added triethylamine (10.4 mL, 7.5 g, 75 mmol) followed by addition of propanoyl chloride (3.6 mL, 3.8 g, 41 mmol) at ca 30°C and stirred for 2 h. The reaction mixture was immersed in pre-heated oil bath at 160°C and stirred for 24 h. at the same temperature. Water was added to the reaction mixture and extracted with ethyl acetate (3 + 100 mL). The organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The crude compound was crystallised from diisopropyl ether to yield the title compound (11.8 g, 72%).

mp: 86-88°C.

^{1}H NMR ($CDCl_3$): δ 8.25 (d, J = 7.89 Hz, 1H), 7.80 - 7.60 (m, 2H), 7.43 (t, J = 7.89 Hz, 1H), 7.12 (d, J = 8.62 Hz, 2H), 6.76 (d, J = 8.62 Hz, 2H), 4.54 (t, J = 5.07 Hz, 2H), 4.30 (t, J = 5.07 Hz, 2H),4.15 (q, J = 7.06 Hz, 2H), 3.92 (t, J = 6.4 Hz, 1H), 3.68 - 3.48 (m, 1H), 3.40 - 3.20 (m, 1H), 3.11 (q, J = 7.38 Hz, 2H), 2.91 (d, J = 6.64 Hz, 2H), 1.44 (t, J = 3.8 Hz, 3H), 1.21 (t, J = 7.06 Hz, 3H), 1.14 (t, J = 7.38 Hz, 3H).

Example 28

(±)-2-Ethoxy-3-[4-[2-[2-ethyl-4-oxo-3,4-dihydro-3-quinazolinyl] ethoxy] phenyl]propanoic acid



The title compound (72 mg, 70%) was obtained from (±)-ethyl 2-ethoxy-3-[4-[2-[2-ethyl-4-oxo-3,4-dihydro-3-quinazolinyl]ethoxy]phenyl]propanoate (110 mg, 0.25 mmol) obtained in Example 27 and sodium carbonate (133 mg, 1.25 mmol) by a similar procedure to that described in Example 2.

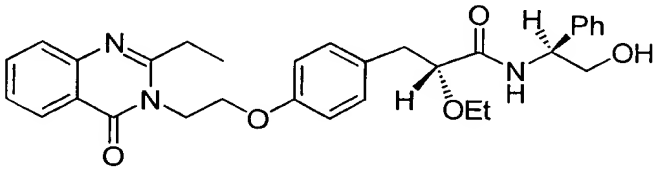
mp 140-141°C.

^{1}H NMR (DMSO-d_6): δ 8.13 (d, J = 7.89 Hz, 1H), 7.82 (t, J = 7.01 Hz, 1H), 7.64 (d, J = 8.21 Hz, 1H), 7.50 (t, J = 7.26 Hz, 1H), 7.13 (d, J = 8.50 Hz, 2H), 6.84 (d, J = 8.50 Hz, 2H), 4.47 (t, J = 5.19 Hz, 2H), 4.26 (t, J = 5.19 Hz, 2H), 3.99 - 3.84 (m,

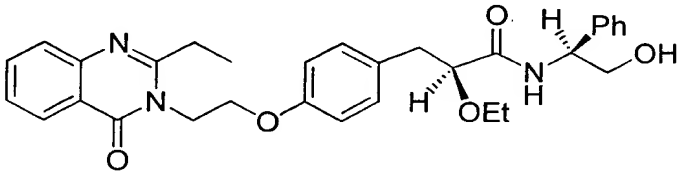
1H), 3.60 - 3.40 (m, 1H), 3.40 - 3.20 (m, 1H), 3.06 (q, J = 6.96 Hz, 2H), 2.88 (q, J = 6.64 Hz, 2H), 1.32 (t, J = 7.17 Hz, 3H), 1.02 (t, J = 6.96 Hz, 3H).

Example 29

[2R, N(1S)] 2-ethoxy-3-[4-[2-[2-ethyl-4-oxo-3,4-dihydro-3-quinazolinyl]ethoxy]-N-(2-hydroxy-1-phenylethyl)propanamide (29a)



[2S, N(1S)] 2-ethoxy-3-[4-[2-[2-ethyl-4-oxo-3,4-dihydro-3-quinazolinyl]ethoxy]phenyl]-N-(2-hydroxy-1-phenylethyl)propanamide (29b)



The title compounds [2R, N(1S)] propanamide (**29a**) and [2S, N(1S)] propanamide (**29b**) were obtained from (±)-2-ethoxy-3-[4-[2-[2-ethyl-4-oxo-3,4-dihydro-3-quinazolinyl]ethoxy]phenyl]propanoic acid (187 mg, 0.45 mmol) obtained in Example 28, triethylamine (288 μL, 2.05 mmol), pivaloyl chloride (61 μL, 0.5 mmol) and S-(+)-2-phenylglycinol (62 mg, 0.45 mmol) by a similar procedure to that described in Example 4.

Spectral data for **(29a)**:

mp: 128-130°C; $[\alpha]_D^{25}$ = + 46.1 (c = 1.0, MeOH).

^{1}H NMR ($CDCl_3$): δ 8.26 (d, J = 7.89 Hz, 1H), 7.80 - 7.68 (m, 2H), 7.46 (t, J = 7.24 Hz, 1H), 7.38 - 6.96 (m, 7H), 6.79 (d, J = 8.49 Hz, 2H), 5.01 - 4.90 (m, 1H), 4.56 (t, J = 4.98 Hz, 2H), 4.34 (t, J = 4.98 Hz, 2H), 3.95 (dd, J = 3.80 and 6.66 Hz, 1H), 3.68 (d, J = 5.40 Hz, 2H), 3.48 (q, J = 6.95 Hz, 2H), 3.21 - 3.10 (m, 2H), 3.10 - 2.84 (m, 2H), 1.46 (t, J = 7.31 Hz, 3H), 1.13 (t, J = 7.05 Hz, 3H).

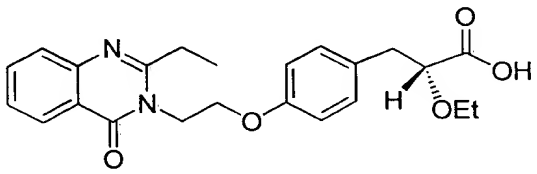
Spectral data for **(29b)**:

mp: 156-158°C; $[\alpha]_D^{25}$ = + 4.1 (c = 1.0, MeOH).

^{1}H NMR ($CDCl_3$): δ 8.28 (d, J = 7.89 Hz, 1H), 7.81 - 7.68 (m, 2H), 7.46 (t, J = 7.24 Hz, 1H), 7.26 - 7.00 (m, 7H), 6.70 (d, J = 8.49 Hz, 2H), 5.02 - 4.91 (m, 1H), 4.57 (t, J = 5.14 Hz, 2H), 4.30 (t, J = 5.14 Hz, 2H), 3.98 (dd, J = 3.80 and 6.66 Hz, 1H), 3.85 (d, J = 4.25 Hz, 2H), 3.60 - 3.45 (m, 2H), 3.16 (q, J = 7.19 Hz, 2H), 3.10 - 2.80 (m, 2H), 1.47 (t, J = 7.36 Hz, 3H), 1.17 (t, J = 7.01 Hz, 3H).

Example 30

(+)-2-Ethoxy-3-[4-[2-[2-ethyl-4-oxo-3,4-dihydro-3-quinazolinyl]ethoxy]phenyl] propanoic acid



The title compound (83 mg, 71 %) was obtained from [2R, N(1S)] 2-ethoxy-3-[4-[2-[2-ethyl-4-oxo-3,4-dihydro-3-quinazolinyl]ethoxy]phenyl]-N-(2-hydroxy-1-phenylethyl)propanamide (150 mg, 0.283 mmol) obtained in Example **29a** by a similar procedure to that described in Example 6.

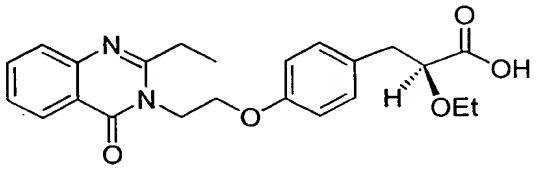
mp: 120-122°C.

$[\alpha]_D^{25}$ = + 19.2 (c = 1.0, MeOH).

^{1}H NMR ($CDCl_3$): δ 8.24 (d, J = 7.88 Hz, 1H), 7.80 - 7.63 (m, 2H), 7.43 (t, J = 7.21 Hz, 1H), 7.11 (d, J = 8.63 Hz, 2H), 6.77 (d, J = 8.63 Hz, 2H), 4.53 (t, J = 4.98 Hz, 2H), 4.30 (t, J = 4.98 Hz, 2H), 4.01 (dd, J = 4.47 and 7.38 Hz, 1H), 3.69 - 3.34 (m, 2H), 3.19 - 2.85 (m, 4H), 1.42 (t, J = 7.42 Hz, 3H), 1.14 (t, J = 6.94 Hz, 3H).

Example 31

(-)-2-Ethoxy-3-[4-[2-[2-ethyl-4-oxo-3,4-dihydro-3-quinazolinyl]ethoxy]phenyl]propanoic acid



The title compound (170 mg, 82 %) was obtained from [2S, N(1S)] 2-ethoxy-3-[4-[2-[2-ethyl-4-oxo-3,4-dihydro-3-quinazolinyl]ethoxy]phenyl]-N-(2-hydroxy-1-

phenylethyl)propanamide (267 mg, 0.504 mmol) obtained in Example **29b** by a similar procedure to that described in Example 6.

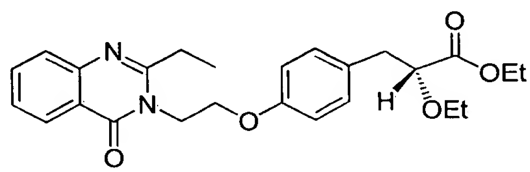
mp: 134-136°C

$[\alpha]_D^{25}$ = -19.2 (c = 1.0, MeOH).

^{1}H NMR ($CDCl_3$): δ 8.24 (d, J = 7.89 Hz, 1H), 7.79 - 7.61 (m, 2H), 7.43 (t, J = 7.66 Hz, 1H), 7.11 (d, J = 8.63 Hz, 2H), 6.77 (d, J = 8.63 Hz, 2H), 4.53 (t, J = 4.98 Hz, 2H), 4.31 (t, J = 4.98 Hz, 2H), 4.02 (dd, J = 4.22 and 7.12 Hz, 1H), 3.61 - 3.32 (m, 2H), 3.16 - 2.82 (m, 4H), 1.43 (t, J = 7.36 Hz, 3H), 1.15 (t, J = 6.96 Hz, 3H).

Example 32

(+)-Ethyl 2-ethoxy-3-[4-[2-[2-ethyl-4-oxo-3,4-dihydro-3-quinazolinyl]ethoxy]phenyl] propanoate



To a stirred suspension of potassium carbonate (172 mg, 1.24 mmol) in DMF (2 mL) was added a solution of (+)-2-ethoxy-3-[4-[2-[2-ethyl-4-oxo-3,4-dihydro-3-quinazolinyl]ethoxy]phenyl]propanoic acid (256 mg, 0.624 mmol) obtained in Example 30 in dry DMF (2 mL) and stirred at ca 30°C for 30 min. To this reaction mixture was added ethyl bromide (93 mL, 1.24 mmol) slowly dropwise and stirred for 1 h at *ca* 30°C. The reaction mixture was poured into water (15 mL) and extracted with ethyl acetate (2 x 15 mL). The combined ethyl acetate extracts were washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by column chromatography using ethyl acetate and pet ether (4 : 6) as eluent to afford the title compound (92 mg, 86 %).

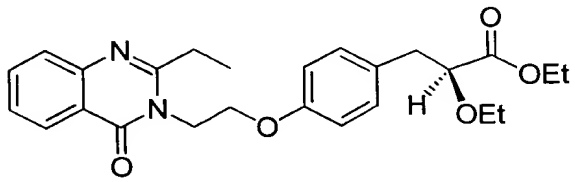
mp: 114-116 °C.

$[\alpha]_D^{25}$ = 11.1 (c = 1.0, MeOH).

^{1}H NMR ($CDCl_3$) δ 8.26 (d, J = 7.88 Hz, 1H), 7.66 - 7.85 (m, 2H), 7.45 (t, J = 6.68 Hz, 1H), 7.13 (d, J = 8.39 Hz, 2H), 6.78 (d, J = 8.62 Hz, 2H), 4.55 (t, J = 5.14 Hz, 2H), 4.32 (t, J = 5.03 Hz, 2H), 4.16 (q, J = 7.09 Hz, 2H), 3.93 (t, J = 6.57 Hz, 1H), 3.69 - 3.50 (m, 1H), 3.42 - 3.25 (m, 1H), 3.12 (q, J = 7.36 Hz, 2H), 2.93 (d, J = 6.55 Hz, 2H), 1.45 (t, J = 7.33 Hz, 3H), 1.32 - 1.11 (m, 6H).

Example 33

(-)-Ethyl 2-ethoxy-3-[4-[2-[2-ethyl-4-oxo-3,4-dihydro-3-quinazolinyl]ethoxy] phenyl]propanoate



The title compound (75 mg, 70%) was obtained from (-)-2-ethoxy-3-[4-[2-[2-ethyl-4-oxo-3,4-dihydro-3-quinazolinyl]ethoxy]phenyl]propanoic acid (100 mg, 0.243 mmol) obtained in Example 31, ethyl bromide (36 mL, 0.487 mmol) and potassium carbonate as a base by a similar procedure to that described in Example 32.

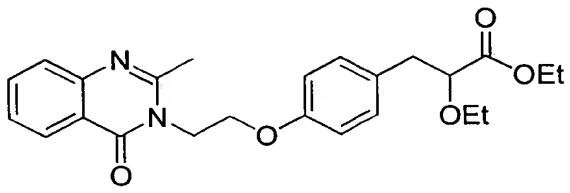
mp: 108-110°C

$[\alpha]_D^{25}$ = - 11.68 (c = 0.50, MeOH).

^{1}H NMR ($CDCl_3$): δ 8.26 (d, J = 7.47 Hz, 1H), 7.83 - 7.64 (m, 2H), 7.45 (t, J = 7.26 Hz, 1H), 7.13 (d, J = 8.62 Hz, 2H), 6.78 (d, J = 8.62 Hz, 2H), 4.55 (t, J = 5.14 Hz, 2H), 4.32 (t, J = 5.03 Hz, 2H), 4.16 (q, J = 7.10 Hz, 2H), 3.93 (t, J = 6.55 Hz, 1H), 3.69 - 3.51 (m, 1H), 3.42 - 3.26 (m, 1H), 3.12 (q, J = 7.38 Hz, 2H), 2.93 (d, J = 6.59 Hz, 2H), 1.45 (t, J = 7.33 Hz, 3H), 1.30 - 1.11 (m, 6H).

Example 34

(±)-Ethyl 2-ethoxy-3-[4-[2-[2-methyl-4-oxo-3,4-dihydro-3-quinazolinyl]ethoxy]phenyl] propanoate



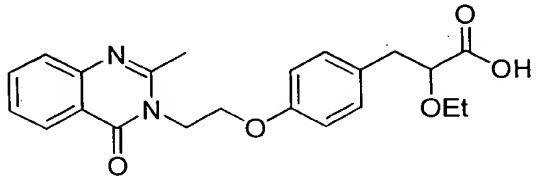
The title compound (229 mg, 33%) was obtained as a liquid from 2-methyl-4-oxo-3,4-dihydroquinazoline (0.25 g, 1.56 mmol), potassium carbonate (431 mg, 3.12 mmol) and (±)-ethyl 2-ethoxy-3-[4-(2-bromoethoxy)phenyl]propanoate (647 mg, 1.87 mmol) (disclosed in U.S. Patent Application Serial No. 09/012,585) by a similar procedure to that described in Example 27.

^{1}H NMR ($CDCl_3$): δ 8.24 (d, J = 8.31 Hz, 1H), 7.79 - 7.60 (m, 2H), 7.44 (t, J = 6.85 Hz, 1H), 7.12 (d, J = 8.63 Hz, 2H), 6.77 (d, J = 8.63 Hz, 2H), 4.52 (t, J = 4.93 Hz,

2H), 4.32 (t, J = 4.82 Hz, 2H), 4.12 (q, J = 5.65 Hz, 2H), 3.92 (t, J = 6.64 Hz, 1H), 3.63 - 3.50 (m, 1H), 3.39 - 3.21 (m, 1H), 2.92 (d, J = 6.65 Hz, 2H), 2.81 (s, 3H), 1.29 - 1.09 (m, 6H).

Example 35

(±)-2-Ethoxy-3-[4-[2-[2-methyl-4-oxo-3,4-dihydro-3-quinazolinyl]ethoxy]phenyl] propanoic acid



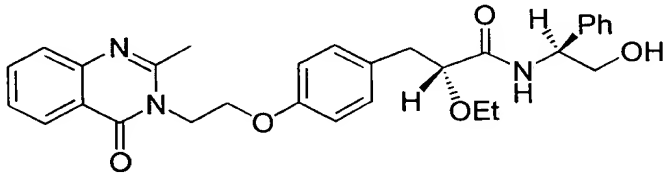
The title compound (100 mg, 61%) was obtained from (±)-ethyl 2-ethoxy 3-[4-[2-[2-methyl-4-oxo-3,4-dihydro-3-quinazolinyl]ethoxy]phenyl]propanoate (175 mg, 0.41 mmol) obtained in Example 34 and sodium carbonate (219 mg, 2.06 mmol) by a similar procedure to that described in Example 2.

mp: 124-126 °C.

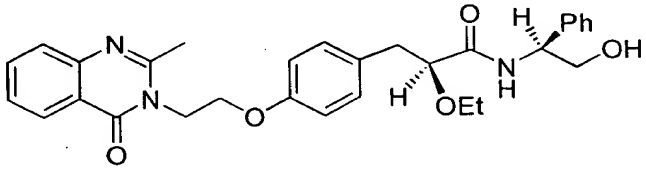
^{1}H NMR ($CDCl_3$): δ 8.25 (d, J = 7.89 Hz, 1H), 7.79 - 7.60 (m, 2H), 7.45 (t, J = 7.47 Hz, 1H), 7.13 (d, J = 8.62 Hz, 2H), 6.79 (d, J = 8.62 Hz, 2H), 4.53 (t, J = 4.82 Hz, 2H), 4.33 (t, J = 4.98 Hz, 2H), 4.08 - 3.99 (m, 1H), 3.62 - 3.39 (m, 2H), 3.12 - 2.86 (m, 2H), 2.81 (s, 3H), 1.16 (t, J = 7.05 Hz, 3H).

Example 36

[2R, N(1S)] 2-ethoxy-3-[4-[2-[2-methyl-4-oxo-3,4-dihydro-3-quinazolinyl]ethoxy]phenyl]-N-(2-hydroxy-1-phenylethyl)propanamide (36a) :



[2S, N(1S)] 2-ethoxy-3-[4-[2-[2-methyl-4-oxo-3,4-dihydro-3-quinazolinyl]ethoxy]phenyl]-N-(2-hydroxy-1-phenylethyl)propanamide (36b) :



The title compounds [2R, N(1S)] propanamide (**36a**) and [2S, N(1S)] propanamide (**36b**) were obtained from (±)-2-ethoxy-3-[4-[2-[2-methyl-4-oxo-3,4-dihydro-3-quinazolinyl]ethoxy]phenyl]propanoic acid (1.5 g, 3.78 mmol) obtained in Example 35, triethylamine (2.37 mL, 16.87 mmol), pivaloyl chloride (0.56 mL, 4.17 mmol) and S-(+)-2-phenylglycinol (520 mg, 3.78 mmol) by a similar procedure to that described in Example 4.

Spectral data for **(36a)**:

mp: 150-152 °C. $[\alpha]_D^{25}$ = 43.0 (c = 0.4, MeOH).

^{1}H NMR ($CDCl_3$): δ 8.23 (d, J = 7.89 Hz, 1H), 7.79 - 7.59 (m, 2H), 7.43 (t, J = 7.89 Hz, 1 H), 7.79 – 7.59 (m, 7H), 7.43 (t, J = 8.4 Hz, 2H), 4.99 – 4.90 (m, 1 H), 4.52 (t, J = 4.82 Hz, 2 H), 4.33 (t, J = 4.82 Hz, 2 H), 3.93 (dd, J = 6.18 and 3.78 Hz, 1 H), 3.69 – 3.60 (m, 2H), 3.45 (q, J = 7.02 Hz, 2H), 3.08 (dd, J = 16.11 and 3.74 Hz, 1 H), 2.91 (dd, J = 14.11 and 6.46 Hz, 1 H), 2.81 (s, 3 H), 1.10 (t J = 6.94 Hz, 3 H).

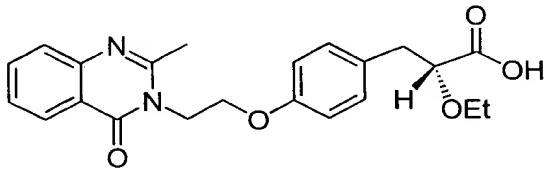
Spectral data for **(36b)**:

mp: 158-160 °C. $[\alpha]_D^{25}$ = 7.5 (c = 0.4, MeOH).

^{1}H NMR ($CDCl_3$): δ 8.27 (d, J = 7.89 Hz, 1H), 7.80 – 7.61 (m, 2H), 7.45 (t, J = 7.38 Hz, 1H), 7.29 – 6.99 (m, 7H), 6.70 (d, J = 8.67 Hz, 2H), 5.01 – 4.92 (m, 1H), 4.55 (t, J = 4.93 Hz, 2H), 4.31 (t, J = 4.93 Hz, 2H), 3.97 (dd, J = 6.59 and 3.88 Hz, 1H), 3.88 – 3.80 (m, 2H), 3.59 – 3.43 (m, 2H), 3.05 (dd, J = 14.11 and 3.50 Hz, 1H), 2.92 – 2.80 (m, 3H), 2.82 (s, 3H), 1.17 (t, J = 6.94 Hz, 2H)

Example 37

(+)-2-Ethoxy-3-[4-[2-[2-methyl-4-oxo-3,4-dihydro-3-quinazolinyl]ethoxy]phenyl] propanoic acid



The title compound (330 mg, 81%) was obtained from [2R, N(1S)] 2-ethoxy-3-[4-[2-[2-methyl-4-oxo-3,4-dihydro-3-quinazolinyl]ethoxy]phenyl]-N-(2-hydroxy-1-phenylethyl]propanamide (530 mg, 1.03 mmol) obtained in Example **36a** by a similar procedure to that described in Example 6.

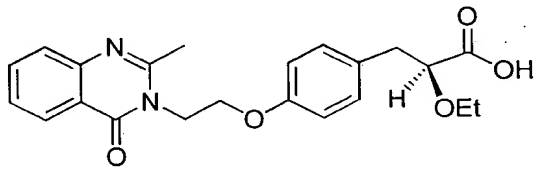
mp: 110 - 112 °C.

$[\alpha]_D^{25}$ = 16.7 (c = 1.0, MeOH).

^{1}H NMR ($CDCl_3$) : δ 8.23 (d, J = 7.89 Hz, 1H), 7.79 - 7.60 (m, 2H), 7.43 (t, J = 7.31 Hz, 1H), 7.13 (d, J = 8.3 Hz, 2H), 6.77 (d, J = 8.39 Hz, 2H), 4.52 (t, J = 4.77 Hz, 2H), 4.31 (t, J = 4.77 Hz, 2H), 4.00 (dd, J = 7.47 and 4.56 Hz, 1H), 3.66 - 3.31 (m, 2H), 3.05 (dd, J = 14.16, 4.5 Hz, 1H), 2.89 (dd, J = 14.16, 7.47 Hz, 1H), 2.81 (s, 3H), 1.15 (t, J = 7.01 Hz, 3H).

Example 38

(-)-2-Ethoxy-3-[4-[2-[2-methyl-4-oxo-3,4-dihydro-3-quinazolinyl]ethoxy]phenyl] propanoic acid :



The title compound (340 mg, 78%) was obtained from [2S, N(1S)]-2-ethoxy-3-[4-[2-[2-methyl-4-oxo-3,4-dihydro-3-quinazolinyl]ethoxy]phenyl]-N-(2-hydroxy-1-phenylethyl)propanamide (570 mg, 1.1 mmol) obtained in Example **36b** by a similar procedure to that described in Example 6.

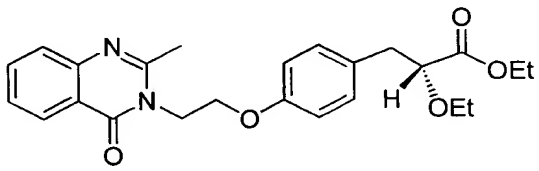
mp: 132-134°C

$[\alpha]_D^{25}$ = -16.4 (c = 1.0, MeOH).

^{1}H NMR ($CDCl_3$): δ 8.24 (d, J = 7.89 Hz, 1H), 7.78 – 7.60 (m, 2H), 7.43 (t, J = 7.35 Hz, 1H), 7.12 (d, J = 8.53 Hz, 2H), 6.77 (d, J = 8.49 Hz, 2H), 4.52 (t, J = 4.88 Hz, 2H), 4.32 (t, J = 4.93 Hz, 2H), 4.01 (dd, J = 7.4 and 4.54 Hz, 1H), 3.65 – 3.31 (m, 2H), 3.05 (dd, J = 14.11 and 4.47 Hz, 1H), 2.92 (dd,14.11 and 7.47 Hz, 1H), 2.81 (s, 3H), 1.15 (t, J = 6.96 Hz, 3H).

Example 39

(+)-Ethyl 2-ethoxy-3-[4-[2-[2-methyl-4-oxo-3,4-dihydro-3-quinazolinyl]ethoxy] phenyl] propanoate



The title compound (50 mg, 78%) was obtained from (+)-2-ethoxy-3-[4-[2-[2-methyl-4-oxo-3,4-dihydro-3-quinazolinyl]ethoxy]phenyl]propanoic acid (60 mg, 0.15 mmol) obtained in Example 37, potassium carbonate (42 mg, 0.30 mmol), and ethyl bromide (33 mg, 0.30 mmol) by a similar procedure to that described in Example 32.

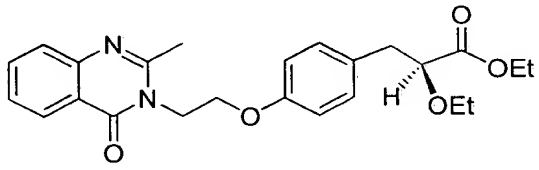
mp: 108-110°C.

$[\alpha]_D^{25} = 12.8$ (c = 0.5, MeOH).

^{1}H NMR ($CDCl_3$) : δ 8.26 (d, J = 8.3 Hz, 1H), 7.80 – 7.60 (m, 2H), 7.46 (t, J = 7.47 Hz, 1H), 7.15 (d, J = 8.3 Hz, 2H), 6.79 (d, J = 8.42 Hz, 2H), 4.54 (t, J = 4.81 Hz, 2H), 4.34 (t, J = 4.82 Hz, 2H), 4.17 (q, J = 7.05 Hz, 2H), 3.94 (t, J = 6.59 Hz, 1H), 3.68 – 3.50 (m, 1H), 3.41 – 3.22 (m, 1H), 2.94 (d, J = 6.44 Hz, 2H), 2.84 (s, 3H), 1.30 – 1.10 (m, 6H).

Example 40

(-)-Ethyl 2-ethoxy-3-[4-[2-[2-methyl-4-oxo-3,4-dihydro-3-quinazolinyl]ethoxy]phenyl] propanoate



The title compound (51 mg, 79%) was obtained from (-)-2-ethoxy-3-[4-[2-[2-methyl-4-oxo-3,4-dihydro-3-quinazolinyl]ethoxy]phenyl]propanoic acid (60 mg, 0.15 mmol) obtained in Example 38, ethyl bromide (33 mg, 0.30 mmol) and potassium carbonate (42 mg, 0.30 mmol) as a base by a similar procedure to that described in Example 32.

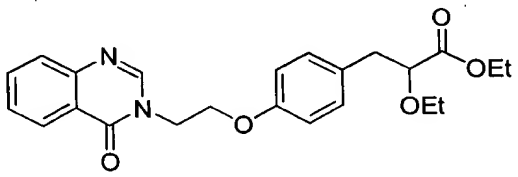
mp: 112-114°C

$[\alpha]_D^{25} = 12.8$ (c = 0.50, MeOH).

^{1}H NMR ($CDCl_3$): δ 8.27 (d, J = 7.89 Hz, 1H), 7.80 – 7.61 (m, 2H), 7.46 (t, J = 7.42 Hz, 1H), 7.15 (d, J = 8.10 Hz, 2H), 6.79 (d, J = 8.63 Hz, 2H), 4.54 (t, J = 4.89 Hz, 2H), 4.34 (t, J= 4.82 Hz, 2H), 4.17 (q, J = 7.09 Hz, 2H), 3.94 (t, J = 6.64 Hz, 1H), 3.69 – 3.51 (m, 1H), 3.40 – 3.23 (m, 1H), 2.94 (d, J = 6.31 Hz, 2H), 2.84 (s, 3H), 1.32 – 1.11 (m, 6H).

Example 41

(±)-Ethyl 2-ethoxy-3-[4-[2-[4-oxo-3,4-dihydro-3-quinazolinyl]ethoxy] phenyl]propanoate



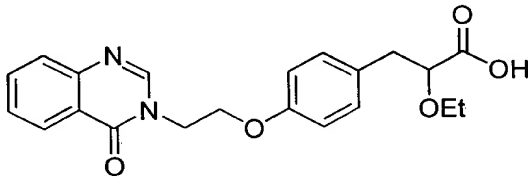
The title compound (525 mg, 62%) was obtained from 4-oxo-3,4-dihydro-quinazoline (300 mg, 2.05 mmol), potassium carbonate (0.567 g, 4.1 mmol) and ethyl 2-ethoxy-3-[4-(2-bromoethoxy)phenyl]propanoate (0.851 g, 2.46 mmol) (disclosed in U.S. Patent Application Serial No. 09/012,585), by a similar procedure to that described in Example 27.

mp: 90-92°C.

^{1}H NMR ($CDCl_3$): δ 8.30 (d, J = 8.3 Hz, 1H), 8.21 (s, 1H), 7.81 - 7.71 (m, 2H), 7.50 (t, J = 6.22 Hz, 1H), 7.12 (d, J = 8.39 Hz, 2H), 6.78 (d, J = 8.39 Hz, 2H), 4.40 (t, J = 4.77 Hz, 2H), 4.27 (t, J = 4.61 Hz, 2H), 4.14 (q, J = 7.11 Hz, 2H), 3.92 (t, J = 6.64 Hz, 1H), 3.68 - 3.51 (m, 1H), 3.40 - 3.22 (m, 1H), 2.91 (d, J = 6.64 Hz, 2H), 1.29 - 1.10 (m, 6H).

Example 42

(±)-2-Ethoxy-3-[4-[2-[4-oxo-3,4-dihydro-3-quinazolinyl]ethoxy]phenyl]propanoic acid



The title compound (125 mg, 67%) was obtained from (±)-ethyl 2-ethoxy-3-[4-[2-[4-oxo-3,4-dihydro-3-quinazolinyl]ethoxy]phenyl]propanoate (0.2 g, 0.487 mmol) obtained in Example 41 and sodium carbonate (0.258 g, 2.44 mmol) by a similar procedure to that described in Example 2.

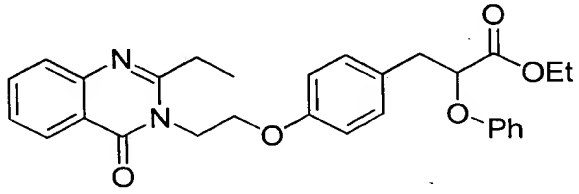
mp: 160-162°C.

^{1}H NMR ($CDCl_3$): δ 8.42 (s, 1H), 8.19 (d, J = 7.89 Hz, 1H), 7.86 (t, J = 7.63 Hz, 1H), 7.71 (d, J = 7.98 Hz, 1H), 7.58 (t, J = 7.47 Hz, 1H), 7.13 (d, J = 7.98 Hz, 2H),

6.86 (d, J = 7.98 Hz, 2H), 4.38 (d, J = 4.98 Hz, 2H), 4.28 (d, J = 4.66 Hz, 2H), 3.93 (t, J = 6.27 Hz, 1H), 3.58 - 3.42 (m, 2H), 2.82 (d, J = 7.98 Hz, 2H), 1.03 (t, J = 7.05 Hz, 3H).

Example 43

(±)-Ethyl 2-phenoxy-3-[4-[2-[2-ethyl-4-oxo-3,4-dihydro-3-quinazolinyl]ethoxy]phenyl] propanoate



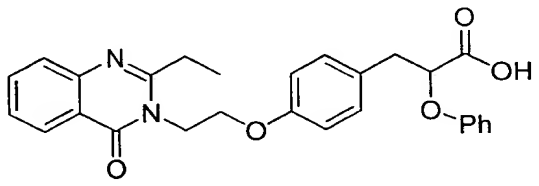
The title compound (140 mg, 20%) was obtained from (±)-2-ethyl-4-oxo-3,4-dihydroquinazoline (250 mg, 1.43 mmol), potassium carbonate (396 mg, 2.87 mmol) and ethyl 2-phenoxy-3-[4-(2-bromoethoxy)phenyl]propanoate (677 mg, 1.72 mmol) by a similar procedure to that described in Example 27.

mp: 142-144°C.

^{1}H NMR ($CDCl_3$): δ 8.20 (d, J 8.30 Hz, 1H), 7.60 (t, J = 5.44 Hz, 2H), 7.45 (t, J = 6.73 Hz, 1H), 7.28 - 7.12 (m, 4H), 6.90 (t, J = 6.25 Hz, 1H), 6.81 - 6.71 (m, 4H), 4.70 (m, 1H), 4.52 (t, J = 5.64 Hz, 2H), 4.26 (t, J = 5.19 Hz, 2H), 4.14 (q, J = 7.09 Hz, 2H), 3.18 - 3.00 (m, 4H), 1.42 (t, J = 7.36 Hz, 3H), 1.17 (t, J = 7.08 Hz, 3H).

Example 44

(±)-2-Phenoxy-3-[4-[2-[2-ethyl-4-oxo-3,4-dihydro-3-quinazolinyl]ethoxy]phenyl]propanoic acid



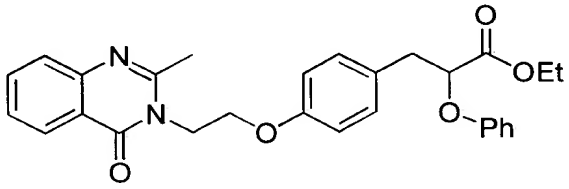
The title compound (80 mg, 0.17 mmol) was obtained from (±)-ethyl 2-phenoxy-3-[4-[2-[2-ethyl-4-oxo-3,4-dihydro-3-quinazolinyl]ethoxy]phenyl]propanoate (150 mg, 0.308 mmol) obtained in Example 43 and sodium carbonate (163 mg, 1.54 mmol) by a similar procedure to that described in Example 2.

mp: 174-176°C.

^{1}H NMR (DMSO-d_6) : δ 8.13 (d, J = 7.89 Hz, 1H), 7.78 (t, J = 7.93 Hz, 1H), 7.62 (d, J = 8.21 Hz, 1H), 7.51 (t, J = 7.42 Hz, 1H), 7.36 - 7.20 (m, 4H), 6.99 - 6.80 (m, 5H), 4.83 (m, 1H), 4.47 (t, J = 6.30 Hz, 2H), 4.27 (t, J = 5.08 Hz, 2H), 3.15 - 3.00 (m, 4H), 1.32 (t, J = 7.10 Hz, 3H).

Example 45

(±)-Ethyl 2-phenoxy-3-[4-[2-[2-methyl-4-oxo-3,4-dihydro-3-quinazolinyl]ethoxy]phenyl] propanoate



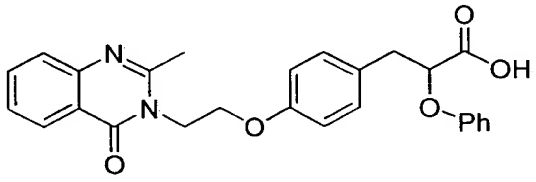
The title compound (950 mg, 42%) was obtained from 2-methyl-4-oxo-3,4-dihydroquinazoline (760 mg, 4.77 mmol), ethyl 2-phenoxy-3-[4-(2-bromoethoxy) phenyl]propanoate (2250 mg, 5.72 mmol) and potassium carbonate (1.32 g, 9.55 mmol) as a base by a similar procedure to that described in Example 27.

mp: 98-00°C.

^{1}H NMR ($CDCl_3$): δ 8.23 (d, J = 8.12 Hz, 1H), 7.78 - 7.58 (m, 2H), 7.43 (t, J = 7.35 Hz, 1H), 7.30 - 7.15 (m, 4H), 6.99 - 6.72 (m, 5H), 4.69 (t, J= 6.43 Hz, 1H), 4.51 (t, J = 4.82 Hz, 2H), 4.30 (t, J = 4.82 Hz, 2H), 4.15 (q, J = 6.09 Hz, 2H), 3.14 (d, J = 6.64 Hz, 2H), 2.08 (s, 3H), 1.69 (t, J = 7.08 Hz, 3H).

Example 46

(±)-2-Phenoxy-3-[4-[2-[2-methyl-4-oxo-3,4-dihydro-3-quinazolinyl] ethoxy] phenyl]propanoic acid



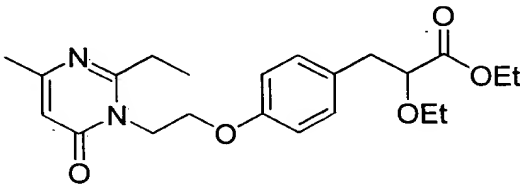
The title compound (90 mg, 64%) was obtained from (±)-ethyl 2-phenoxy-3-[4-[2-[2-methyl-4-oxo-3,4-dihydro-3-quinazolinyl]ethoxy]phenyl]propanoate (150 mg, 0.3 mmol) obtained in Example 45 and sodium carbonate (168 mg, 1.5 mmol) by a similar procedure to that described in Example 2.

mp: 206-210°C.

^{1}H NMR ($CDCl_3$): δ 8.22 (d, J = 7.89 Hz, 1H), 7.72 (t, J = 6.89 Hz, 1H), 7.60 (d, J = 7.89 Hz, 1H), 7.43 (t, J = 7.36 Hz, 1H), 7.27 - 7.11 (m, 4H), 6.94 - 6.71 (m, 5H), 4.67 (t, J = 6.29 Hz, 1H), 4.51 (t, J = 4.9 Hz, 2H), 4.30 (t, J = 4.93 Hz, 2H), 3.17 (d, J = 5.82 Hz, 2H), 2.80 (s, 3H).

Example 47

(±)-Ethyl 2-ethoxy-3-[4-[2-[2-ethyl-4-methyl-6-oxo-1-pyrimidinyl] ethoxy] phenyl]propanoate

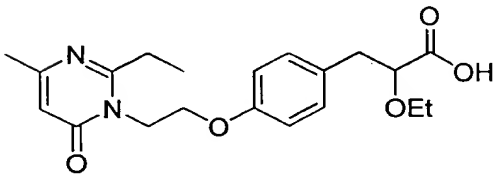


The title compound (430 mg, 59%) was obtained as a liquid from (±)-2-ethyl-4-methyl-6-pyrimidone (250 mg, 1.81 mmol) and ethyl 2-ethoxy-3-[4-(2-bromo-ethoxy)phenyl]propanoate (750 mg, 2.17 mmol) (disclosed in U.S. Patent Application Serial No. 09/012,585), sodium hydride (44 mg, 1.9 mmol, 95 %) as a base, by a similar procedure to that described in Example 27.

^{1}H NMR ($CDCl_3$): δ 7.16 (d, J = 8.62 Hz, 2H), 6.86 (d, J = 8.62 Hz, 2H), 6.43 (s, 1H), 4.70 (t, J = 4.77 Hz, 2H), 4.28 (t, J = 4.77 Hz, 2H), 4.17 (q, J = 7.11 Hz, 2H), 3.96 (t, J = 6.55 Hz, 1H), 3.70 - 3.50 (m, 1H), 3.42 - 3.22 (m, 1H), 2.95 (d, J = 6.55 Hz, 2H), 2.83 (q, J = 7.60 Hz, 2H), 2.40 (s, 3H), 1.32 (t, J = 7.60 Hz, 3H), 1.23 (t, J = 7.11 Hz, 3H), 1.63 (q, J = 6.90 Hz, 3H).

Example 48

(±)-2-Ethoxy-3-[4-[2-[2-ethyl-4-methyl-6-oxo-1-pyrimidinyl]ethoxy]phenyl] propanoic acid



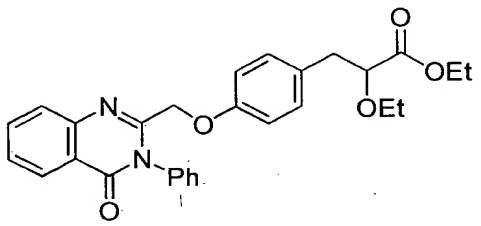
The title compound (100 mg, 50%) was obtained from (±)-ethyl 2-ethoxy-3-[4-[2-[2-ethyl-4-methyl-6-oxo-1-pyrimidinyl]ethoxy]phenyl]propanoate (215 mg, 0.53 mmol) obtained in Example 47 and sodium carbonate (265 mg, 2.5 mmol) by a similar procedure to that described in Example 2.

mp: 100-103°C.

^{1}H NMR ($CDCl_3$): δ 7.19 (d, J = 8.62 Hz, 2H), 6.88 (d, J = 8.62 Hz, 2H), 6.45 (s, 1H), 4.73 (t, J = 4.79 Hz, 2H), 4.30 (t, J = 4.79 Hz, 2H), 4.06 (dd, J = 7.28, 4.56 Hz, 1H), 3.70 - 3.40 (m, 2H), 3.11 (dd, J = 14.16, 4.56 Hz, 1H), 2.97 (dd, J = 14.16 and 7.28 Hz, 1H), 2.85 (q, J = 7.58 Hz, 2H), 2.42 (s, 3H), 1.33 (t, J = 7.58 Hz, 3H), 1.20 (t, J = 7.01 Hz, 3 H).

Example 49

(±)-Ethyl 2-ethoxy-3-[4-[[3-phenyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy] phenyl]propanoate

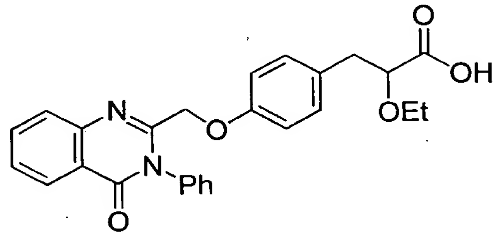


The title compound (420 mg, 87.5%) was obtained as a liquid from (±)-ethyl 2-ethoxy-3-(4-hydroxyphenyl)propanoate (220 mg, 0.92 mmol) (disclosed in U.S. Patent Application Serial No. 09/012,585), 2-chloromethyl-3-phenyl-4-oxo-3,4-dihydroquinazoline (275 mg, 1.01 mmol) and potassium carbonate (383 mg, 2.77 mmol) as a base by a similar procedure to that described in Example 1.

^{1}H NMR ($CDCl_3$) δ 8.30 (d, J = 7.89 Hz, 1H), 7.79 (d, J = 7.83 Hz, 1H), 7.41 - 7.57 (m, 5H), 7.36 (d, J = 7.56 Hz, 2H), 7.07 (d, J = 8.40 Hz, 2H), 6.68 (d, J = 8.40 Hz, 2H), 4.74 (s, 2H), 4.12 (q, J = 7.08 Hz, 2H), 3.93 (t, J = 6.53 Hz, 1H), 3.50 - 3.68 (m, 1H), 3.22 - 3.40 (m, 1H), 2.90 (d, J = 6.65 Hz, 2H), 1.10 - 1.29 (m, 6H).

Example 50

(±)-2-Ethoxy-3-[4-[[3-phenyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl] propanoic acid



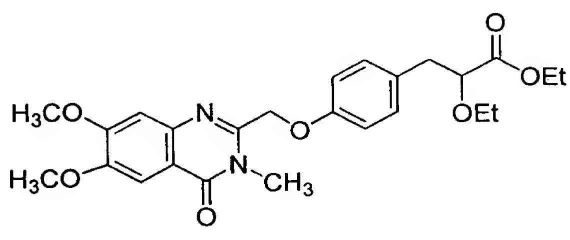
The title compound (120 mg, 58%) was obtained from (±)-ethyl 2-ethoxy-3-[4-[[3-phenyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl]propanoate (220 mg, 0.466 mmol) obtained in Example 49 and sodium carbonate (247 mg, 2.33 mmol) by a similar procedure to that described in Example 2.

mp: 173 °C.

^{1}H NMR (DMSO-d_6) : δ 8.47 (d, J = 8.21 Hz, 1H), 7.87 (d, J = 7.47 Hz, 1H), 7.76 (d, J = 8.39 Hz, 2H), 7.59 (t, J = 7.68 Hz, 1H), 7.41 (t, J = 7.82 Hz, 1H), 7.34 - 7.11 (m, 5H), 6.98 (d, J = 8.39 Hz, 2H), 4.69 (s, 2H), 3.94 (dd, J = 5.12 and 7.42 Hz, 1H), 3.58 - 3.40 (m, 1H), 3.39 - 3.20 (m, 1H), 2.98 - 2.76 (m, 2H), 1.03 (t, J = 7.01 Hz, 3H).

Example 51

(±)-Ethyl 2-ethoxy-3-[4-[[3-methyl-4-oxo-3,4-dihydro-6,7-dimethoxy-2-quinazolinyl]methoxy]phenyl]propanoate

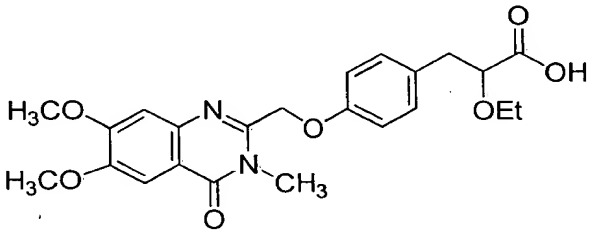


The title compound (420 mg, 79.9%) was obtained as a liquid from (±)-ethyl 2-ethoxy-3-(4-hydroxyphenyl)propanoate (292 mg, 1.23 mmol) (disclosed in U.S. Patent Application Serial No. 09/012,585), 2-chloromethyl-3-methyl-4-oxo-3,4-dihydro-6,7-dimethoxy quinazoline (300 mg, 1.12 mmol) and potassium carbonate (464 mg, 3.36 mmol) as a base by a similar procedure to that described in Example 1.

^{1}H NMR ($CDCl_3$) : δ 7.60 (s, 1H), 7.19 (d, J = 8.63 Hz, 2H), 7.11 (s, 1H), 6.96 (d, J = 8.63 Hz, 2H), 5.12 (s, 2H), 4.15 (q, J = 7.13 Hz, 2H), 4.00 (S,6H) 4.01 - 3.91 (m, 1H), 3.73 (s, 3H), 3.70 - 3.51 (m, 1H), 3.41 - 3.24 (m, 1H), 2.95 (d, J = 6.64 Hz, 2H), 1.28 - 1.10 (m, 6H).

Example 52

(±)- 2-Ethoxy-3-[4-[[3-methyl-4-oxo-3,4-dihydro-6,7-dimethoxy-2-quinazolinyl]methoxy] phenyl]propanoic acid



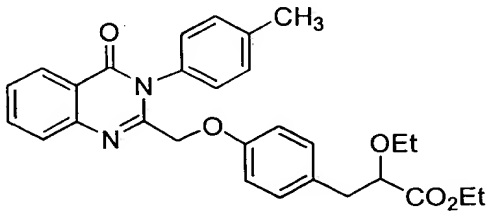
The title compound (300 mg, 79.7%) was obtained from (±)-ethyl 2-ethoxy-3-[4-[[3-methyl-4-oxo-3,4-dihydro-6,7-dimethoxy-2-quinazolinyl]methoxy] phenyl] propanoate (400 mg, 0.85 mmol) obtained in Example 51 and sodium carbonate (451 mg, 4.25 mmol) by a similar procedure to that described in Example 2.

mp: 187°C.

^{1}H NMR ($CDCl_3$): δ 7.61 (s, 1H), 7.19 (d, J = 8.62 Hz, 2H), 7.12 (s, 1H), 6.97 (d, J = 8.62 Hz, 2H), 5.13 (s, 2H), 4.11 - 3.94 (m, 7H), 3.73 (s, 3H), 3.69 - 3.53 (m, 1H), 3.53 - 3.40 (m, 1H), 3.13 - 2.89 (m, 2H), 1.18 (t, J = 6.94 Hz, 3H).

Example 53

(±)-Ethyl 2-ethoxy-3-[4-[[3-(4-methylphenyl)-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl]propanoate



The title compound (310 mg, 60.5%) was obtained from (±)-ethyl 2-ethoxy-3-(4-hydroxy phenyl)propanoate (276 mg, 1.16 mol) (described in U.S. Patent Application Serial No. 09/012,585), 2-chloromethyl-3-(4-methylphenyl)-4-oxo-3,4-

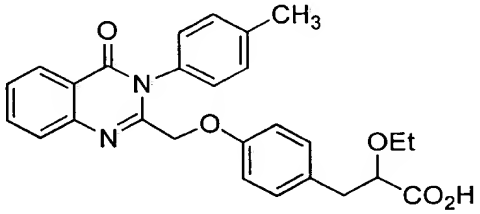
dihydroquinazoline (300 mg, 1.05 mmol) and potassium carbonate (435 mg, 3.16 mmol) as a base by a similar procedure to that described in Example 1.

mp: 81°C.

^{1}H NMR ($CDCl_3$): δ 8.30 (d, J = 7.89 Hz, 1H), 7.79 (d, J = 3.73 Hz, 1H), 7.52 (t, J = 6.09 Hz, 1H), 7.32 - 7.18 (m, 5H), 7.09 (d, J = 8.3 Hz, 2H), 6.72 (d, J = 8.30 Hz, 2H), 4.75 (s, 2H), 4.13(q, J = 7.09 Hz, 2H), 3.93 (t, J = 9.94 Hz, 1H), 3.69 - 3.50 (m, 1H), 3.40 - 3.24 (m, 1H), 2.91 (d, J = 6.41 Hz, 2H), 2.40 (s, 3H), 1.25 - 1.10 (m, 6H).

Example 54

(±)-2-Ethoxy-3-[4-[[3-(4-methylphenyl)-4-oxo-3,4-dihydro-2-quinazolinyl] methoxy]phenyl]propanoic acid



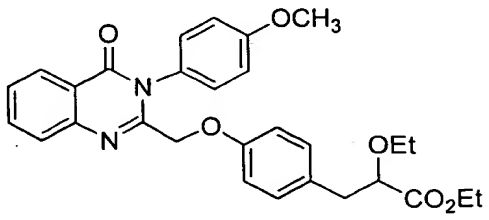
The title compound (85 mg, 69%) was obtained from (±)-ethyl 2-ethoxy-3-[4-[[3-(4-methylphenyl)-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl]propanoate (130 mg, 0.267 mmol) obtained in Example 53 and sodium carbonate (142 mg, 1.33 mmol) by a similar procedure to that described in Example 2.

mp: 178°C.

^{1}H NMR ($CDCl_3$): δ 8.30 (d, J = 7.89 Hz, 1H), 7.79 (d, J = 3.5 Hz, 1H), 7.54 (t, J = 5.97 Hz, 1H), 7.47 - 6.90 (m, 7H), 6.72 (d, J = 8.62 Hz, 2H), 4.74 (s, 2H), 4.01 (dd, J = 4.26 and 7.16 Hz, 1H), 3.64 - 3.30 (m, 2H), 3.09 - 2.88 (m, 2H), 2.39 (s, 3H), 1.12 (t, J = 5.65 Hz, 3H).

Example 55

(±)-Ethyl 2-ethoxy-3-[4-[[3-(4-methoxyphenyl)-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy] phenyl]propanoate

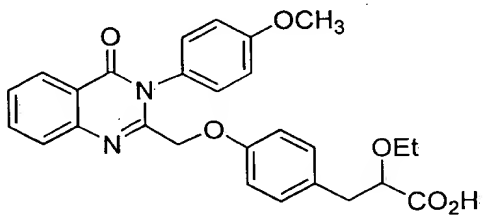


The title compound (350 mg, 60%) was obtained as a liquid from ethyl 2-ethoxy-3-(4-hydroxy phenyl)propanoate (305 mg, 1.28 mmol) (described in U.S.A atent Application Serial No. 09/012,585), 2-chloromethyl-3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazoline (350 mg, 1.16 mmol) and potassium carbonate (482 mg, 3.49 mmol) as a base by a similar procedure to that described in Example 1.

^{1}H NMR ($CDCl_3$): δ 8.30 (d, J = 7.89 Hz, 1H), 7.78 (d, J = 3.73 Hz, 1H), 7.53 (t, J = 6.22 Hz, 2H), 7.23 (d, J = 8.62 Hz, 2H), 7.09 (d, J = 8.21 Hz, 2H), 7.01 (d, J = 8.72 Hz, 2H), 6.72 (d, J = 8.62 Hz, 2H), 4.75 (s, 2H), 4.15 (q, J = 7.13 Hz, 2H), 3.93 (t, J = 6.65 Hz, 1H), 3.82 (s, 3H), 3.64 - 3.50 (m, 1H), 3.40 - 3.22 (m, 1H), 2.91 (d, J = 6.64 Hz, 2H), 1.25 (t, J = 7.10 Hz, 3H), 1.13 (t, J = 7.40 Hz, 3H).

Example 56

(±)-2-Ethoxy-3-[4-[[3-(4-methoxyphenyl)-4-oxo-3,4-dihydro-2-quinazolinyl] methoxy]phenyl]propanoic acid



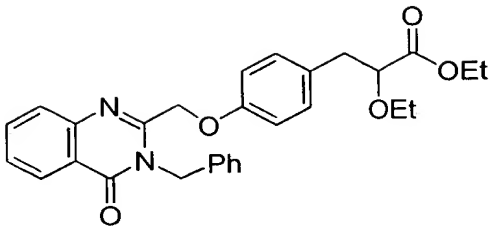
The title compound (200 mg, 78.4%) was obtained from (±)-ethyl 2-ethoxy-3-[4-[[3-(4-methoxy phenyl)-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy] phenyl] propanoate (270 mg, 0.537 mmol) obtained in example 55 and sodium carbonate (285 mg, 2.68 mmol) by a similar procedure to that described in Example 2.

mp: 171°C.

^{1}H NMR ($CDCl_3$): δ 8.32 (d, J = 7.89 Hz, 1H), 7.81 (d, J = 3.41 Hz, 2H), 7.64 - 7.50 (m, 1H), 7.25 (d, J = 8.53 Hz, 2H), 7.29 - 6.92 (m, 4H), 6.74 (d, J = 8.53 Hz, 2H), 4.77 (s, 2H), 4.03 (dd, J = 4.19 and 7.00 Hz, 1H), 3.85 (s, 3H), 3.64 - 3.56 (m, 1H), 3.48 - 3.40 (m, 1H), 3.10 - 2.84 (m, 2H), 1.17 (t, J = 7.01 Hz, 3H).

Example 57

(±)-Ethyl 2-ethoxy-3-[4-[[3-benzyl-4-oxo-3,4-dihydro-2-quinazolinyl] methoxy]phenyl] propanoate

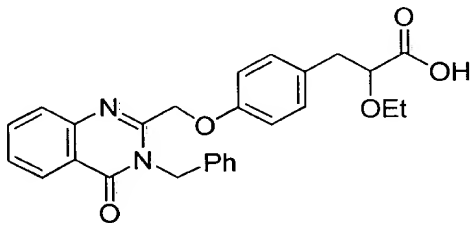


The title compound (450 mg, 75%) was obtained as a liquid from (±)-ethyl 2-ethoxy-3-(4-hydroxyphenyl)propanoate (322 mg, 1.35 mmol) (disclosed in U.S. Patent Application Serial No. 09/012,585), 2-chloromethyl-3-benzyl-4-oxo-3,4-dihydro-quinazoline (350 mg, 1.23 mmol) and potassium carbonate (509 mg, 3.69 mmol) as a base by a similar procedure to that described in Example 1.

^{1}H NMR ($CDCl_3$) : δ 8.35 (d, J = 7.89 Hz, 1H), 7.85 - 7.70 (m, 2H), 7.54 (t, J = 6.36 Hz, 1H), 7.36 - 7.10 (m, 7H), 6.87 (d, J = 8.63 Hz, 2H), 5.59 (s, 2H), 5.00 (s, 2H), 4.15 (q, J = 7.08 Hz, 2H), 3.96 (t, J = 6.57 Hz, 1H), 3.69 - 3.50 (m, 1H), 3.41 - 3.25 (m, 1H), 2.94 (d, J = 6.32 Hz, 2H), 1.29 - 1.11 (m, 6H).

Example 58

(±)-2-Ethoxy-3-[4-[[3-benzyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy] phenyl]propanoic acid



The title compound (280 mg, 80%) was obtained from (±)-ethyl 2-ethoxy-3-[4-[[3-benzyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl]propanoate (370 mg, 0.76 mmol) obtained in Example 57 and sodium carbonate (403 mg, 3.8 mmol) by a similar procedure to that described in Example 2.

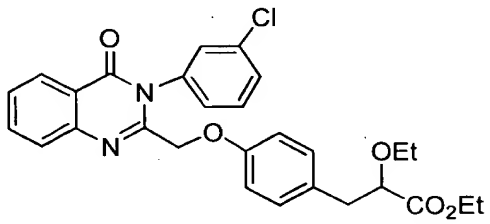
mp: 160°C.

^{1}H NMR ($CDCl_3$): δ 8.35 (d, J = 8.31 Hz, 1H), 7.81 - 7.70 (m, 2H), 7.54 (t, J = 6.43 Hz, 1H), 7.38 - 7.10 (m, 7H), 6.88 (d, J = 8.53 Hz, 2H), 5.59 (s, 2H), 5.01 (s, 2H), 4.05 (dd, J = 4.15 and 7.21 Hz, 1H), 3.66 - 3.39 (m, 2H), 3.09 (dd, J = 4.15 and 14.21 Hz, 1H), 2.94 (dd, J = 7.21 and 14.21 Hz, 1H), 1.17 (t, J = 7.05 Hz, 3H)

WO 98/54170 PCT/US98/09968

Example 59

(±)-Ethyl 2-ethoxy-3-[4-[[3-(3-chlorophenyl)-4-oxo-3,4-dihydro-2-quinazolinyl] methoxy]phenyl]propanoate

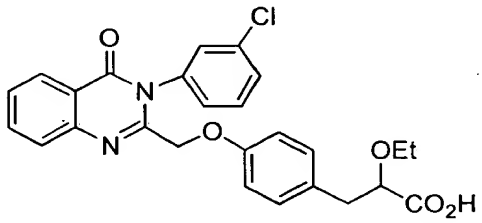


The title compound (300 mg, 49%) was obtained as a liquid from (±)-ethyl 2-ethoxy-3-(4-hydroxyphenyl)propanoate (288 mg, 1.21 mmol), 2-chloromethyl-3-(3-chlorophenyl)-4-oxo-3,4-dihydroquinazoline (370 mg, 1.21 mmol) and potassium carbonate (502 mg, 3.63 mmol) as a base by a similar procedure to that described in Example 1.

^{1}H NMR ($CDCl_3$): δ 8.31 (d, J = 7.88 Hz, 1H), 7.90 - 7.78 (m, 2H), 7.61 - 7.20 (m, 5H), 7.10 (d, J = 8.63 Hz, 2H), 6.71 (d, J = 8.63 Hz, 2H), 4.85 (s, 2H), 4.15 (q, J = 7.07 Hz, 2H), 3.94 (t, J = 6.64 Hz, 1H), 3.70 - 3.51 (m, 1H), 3.41 - 3.25 (m, 1H), 2.92 (d, J = 6.55 Hz, 2H), 1.28 - 1.10 (m, 6H).

Example 60

(±)-2-Ethoxy-3-[4-[[3-(3-chlorophenyl)-4-oxo-3,4-dihydro-2-quinazolinyl] methoxy]phenyl]propanoic acid



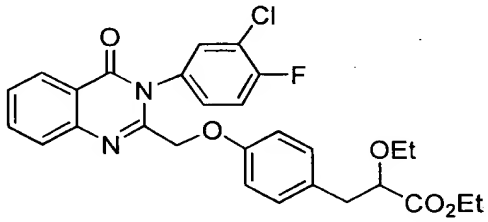
The title compound (125 mg, 66%) was obtained from (±)-ethyl 2-ethoxy-3-[4-[[3-(3-chlorophenyl)-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl]propanoate (200 mg, 0.39 mmol) obtained in Example 59 and sodium carbonate (209 mg, 1.97 mmol) by a similar procedure to that described in Example 2.

mp: 157°C.

^{1}H NMR ($CDCl_3$): δ 8.52 (d, J = 8.31 Hz, 1H), 8.30 (bs, 1H), 7.90 - 7.79 (m, 1H), 7.62 - 6.92 (m, 8H), 6.35 (d, J = 8.3 Hz, 1H), 4.59 (s, 2H), 4.03 (dd, J = 4.47 and 7.05 Hz, 1H), 3.62 - 3.31 (m, 2H), 3.12 - 2.82 (m, 2H), 1.18 (t, J = 3.41 Hz, 3H).

Example 61

(±)-Ethyl 2-ethoxy-3-[4-[[3-(3-chloro-4-fluorophenyl)-4-oxo-3,4-dihydro-2-quinazolinyl] methoxy]phenyl]propanoate

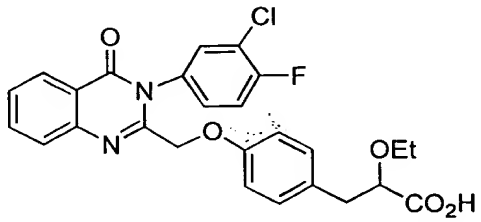


The title compound (250 mg, 57%) was obtained as a liquid from (±)-ethyl 2-ethoxy-3-(4-hydroxyphenyl)propanoate (218 mg, 0.919 mmol) (disclosed in U.S. Patent Application Serial No. 09/012,585, 2-chloromethyl-3-(3-chloro-4-fluoro-phenyl)-4-oxo-3,4-dihydroquinazoline (270 mg, 0.835 mmol) and potassium carbonate (380 mg, 2.5 mmol) as a base by a similar procedure to that described in Example 1.

^{1}H NMR ($CDCl_3$): δ 8.29 (d, J = 7.98 Hz, 1H), 7.77 - 7.83 (m, 2H), 7.50 - 7.60 (m, 1H), 7.44 (d, J = 5.31 Hz, 1H), 7.23 (d, J = 6.32 Hz, 2H), 7.11 (d, J = 8.62 Hz, 2H), 6.71 (d, J = 8.49 Hz, 2H), 4.80 (s, 2H), 4.12 (q, J = 4.75 Hz, 2H), 3.93 (t, J = 6.60 Hz, 1H), 3.50 - 3.68 (m, 1H), 3.24 - 3.41 (m, 1H), 2.91 (d, J = 6.64 Hz, 2H), 1.10 - 1.28 (m, 6H).

Example 62

(±)-2-Ethoxy-3-[4-[[3-(3-chloro-4-fluorophenyl)-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl]propanoic acid



The title compound (85 mg, 50%) was obtained from (±)-ethyl 2-ethoxy-3-[4-[[3-(3-chloro-4-fluorophenyl)-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy] phenyl]

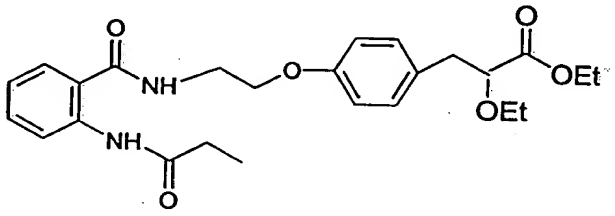
propanoate (180 mg, 0.343 mmol) obtained in Example 61 and sodium carbonate (181 mg, 1.71 mmol) by a similar procedure to that described in Example 2.

mp: 175°C.

^{1}H NMR ($CDCl_3$): δ 8.60 (d, J = 8.07 Hz, 1H), 8.00 (d, J = 4.48 Hz, 1H), 7.70 (d, J = 7.89 Hz, 2H), 7.80 - 7.09 (m, 5H), 6.98 (d, J = 8.39 Hz, 2H), 4.60 (s, 2H), 3.96 (dd, J = 4.61 and 7.43 Hz, 1H), 3.70 - 3.52 (m, 1H), 3.41 - 3.24 (m, 1H), 3.08 - 2.84 (m, 2H), 1.15 (t, J = 6.85 Hz, 3H).

Example 63

(±)-Ethyl 2-ethoxy-3-[4-[2-[N-(2 –propanamido) benzoyl]aminoethoxy] phenyl]propanoate

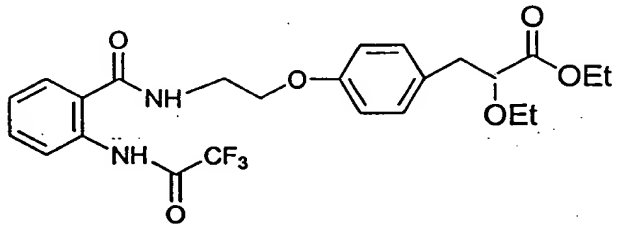


To a stirred solution of (±)-Ethyl 2-ethoxy-3-[4-[2-N-(2-aminobenzoyl) aminoethoxy]phenyl] propanoate (1.5 g, 3.75 mmol) obtained in preparation 6 in a mixture of xylene (5ml) and propanoic acid (5 ml) was added triethylamine (1.04 ml, 0.75 g, 7.5 mmol) followed by addition of propanoyl chloride (0.36 ml, 0.388 g, 4.1 mmol) at *ca* 30°C and stirred 2h. Water was added to the reaction mixture and extracted with ethyl acetate (3 x 10 ml). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The crude compound was chromatographed on silica gel using 20% EtoAC/petroleum ether as eluent to afford the title compound (1.18g, 72%).

^{1}H NMR ($CDCl_3$): δ 8.64 (d, J = 8.63 Hz,1H), 7.51 – 7.42 (m, 2H), 7.18 (d, J = 8.40 Hz,2H), 7.07 (t, J = 7.68 Hz, 1H), 6.84 (d, J = 8.40 Hz, 2H), 4.25 – 4.08 (m, 4H), 3.97 (t, J = 6.57 Hz,1H), 3.88 – 3.80 (m, 2H), 3.70 – 3.52 (m, 1H), 3.42 – 3.26 (m, 1H), 2.96 (d, J = 6.32 Hz, 2H), 2.45 (q, J = 7.53Hz, 2H), 1.32 – 1.10 (m,9H).

Example 64

(±)-Ethyl 2-ethoxy-3-[4-[2-[N-(2 –trifluoroacetamido) benzoyl]aminoethoxy] phenyl]propanoate



The title compound (456 mg, 92%) was obtained from (±)-Ethyl 2-ethoxy-3-[4-[2-N-(2-aminobenzoyl)aminoethoxy]phenyl] propanoate (400mg, 1.0 mmol) obtained in preparation 6 and trifluoroacetic anhydride (314 mg, 1.5 mmol) by a similar procedure described in Example 63.

mp: 70-72°C.

^{1}H NMR ($CDCl_3$): δ 12.72 (bs, D_2O exchangeable, 1H), 8.60 (d, J = 8.30 Hz, 0.5H), 7.68 –7.42 (m, 2H), 7.30 – 7.12 (m, 0.5H), 7.00 – 6.80 (m, 1H), 7.16 (d, J = 8.40 Hz, 2H), 6.83 (d, J = 8.40 Hz, 2H), 4.25 – 4.02 (m, 4H), 3.96 (t, J = 6.55 Hz, 1H), 3.86 (q, J = 5.10 Hz, 2H), 3.70 – 3.42 (m, 1H), 3.42 – 3.20 (m, 1H), 2.95 (d, J = 6.55 Hz, 2H), 1.28 – 1.02 (m, 6H).

The compounds of the present invention lowered random blood sugar level, triglyceride, total cholesterol, LDL, VLDL and increased HDL. This was demonstrated by *in vitro* as well as *in vivo* animal experiments.

Demonstration of Efficacy of Compounds

A) ***In vitro***

a) Determination of hPPARα activity

Ligand binding domain of hPPARα was fused to DNA binding domain of Yeast transcription factor GAL4 in eucaryotic expression vector. Using superfect (Qiagen, Germany) as transfecting reagent HEK-293 cells were transfected with this plasmid and a reporter plasmid harboring the luciferase gene driven by a GAL4 specific promoter. Compound was added at different concentrations after 42 hrs of

transfection and incubated overnight. Luciferase activity as a function of compound binding/activation capacity of PPARα was measured using Packard Luclite kit (Packard, USA) in Top Count (Ivan Sadowski, Brendan Bell, Peter Broag and Melvyn Hollis. Gene. 1992. 118 : 137 –141; Superfect Transfection Reagent Handbook. February, 1997. Qiagen, Germany).

b) Determination of hPPARγ activity

Ligand binding domain of hPPARγ1 was fused to DNA binding domain of Yeast transcription factor GAL4 in eucaryotic expression vector. Using lipofectamine (Gibco BRL, USA) as transfecting reagent HEK-293 cells were transfected with this plasmid and a reporter plasmid harboring the luciferase gene driven by a GAL4 specific promoter. Compound was added at 1 μM concentration after 48 hrs of transfection and incubated overnight. Luciferase activity as a function of drug binding/activation capacity of PPARγ1 was measured using Packard Luclite kit (Packard, USA) in Packard Top Count (Ivan Sadowski, Brendan Bell, Peter Broag and Melvyn Hollis. Gene. 1992. 118 : 137 –141; Guide to Eukaryotic Transfections with Cationic Lipid Reagents. Life Technologies, GIBCO BRL, USA).

Example No	Concentration	PPARα	Concentration	PPARγ
Example 27	50 μM	5	1 μM	19
Example 20	50 μM	5	1 μM	3

c) Determination of HMG CoA reductase inhibition activity

Liver microsome bound reductase was prepared from 2% cholestyramine fed rats at mid-dark cycle. Spectrophotometric assays were carried out in 100 mM KH_2PO_4, 4 mM DTT, 0.2 mM NADPH, 0.3 mM HMG CoA and 125 μg of liver microsomal enzyme. Total reaction mixture volume was kept as 1 ml. Reaction was started by addition of HMG CoA. Reaction mixture was incubated at 37 °C for 30 min and decrease in absorbance at 340 nm was recorded. Reaction mixture without substrate was used as blank (Goldstein, J. L and Brown, M. S. Progress in understanding the LDL receptor and HMG CoA reductase, two membrane proteins that regulate the plasma cholesterol. J. Lipid Res. 1984, 25: 1450 – 1461). The test compounds inhibited the HMG CoA reductase enzyme.

B) In vivo

a) Efficacy in genetic models

Mutation in colonies of laboratory animals and different sensitivities to dietary regimens have made the development of animal models with non-insulin dependent diabetes and hyperlipidemia associated with obesity and insulin resistance possible. Genetic models such as db/db and ob/ob (Diabetes, (1982) 31(1) : 1- 6) mice and zucker fa/fa rats have been developed by the various laboratories for understanding the pathophysiology of disease and testing the efficacy of new antidiabetic compounds (Diabetes, (1983) 32: 830-838 ; Annu. Rep. Sankyo Res. Lab. (1994). 46 : 1-57). The homozygous animals, C57 BL/KsJ-db/db mice developed by Jackson Laboratory, US, are obese, hyperglycemic, hyperinsulinemic and insulin resistant (J. Clin. Invest., (1990) 85 : 962-967), whereas heterozygous are lean and normoglycemic. In db/db model, mouse progressively develops insulinopenia with age, a feature commonly observed in late stages of human type II diabetes when blood sugar levels are insufficiently controlled. The state of pancreas and its course vary according to the models. Since this model resembles that of type II diabetes mellitus, the compounds of the present invention were tested for blood sugar and triglycerides lowering activities.

Male C57BL/KsJ-db/db mice of 8 to 14 weeks age, having body weight range of 35 to 60 grams, bred at Dr. Reddy's Research Foundation (DRF) animal house, were used in the experiment. The mice were provided with standard feed (National Institute of Nutrition (NIN), Hyderabad, India) and acidified water, ad libitum. The animals having more than 350 mg / dl blood sugar were used for testing. The number of animals in each group was 4.

Test compounds were suspended on 0.25 % carboxymethyl cellulose and administered to test group at a dose of 0.001 mg to 30 mg / kg through oral gavage daily for 6 days. The control group received vehicle (dose 10 ml / kg). On 6th day the blood samples were collected one hour after administration of test compounds / vehicle for assessing the biological activity.

The random blood sugar and triglyceride levels were measured by collecting blood (100 µl) through orbital sinus, using heparinised capillary in tubes containing

EDTA which was centrifuged to obtain plasma. The plasma glucose and triglyceride levels were measured spectrometrically, by glucose oxidase and glycerol-3-PO_4 oxidase/peroxidase enzyme (Dr. Reddy's Lab. Diagnostic Division Kits, Hyderabad, India) methods respectively.

The blood sugar and triglycerides lowering activities of the test compound was calculated according to the formula.

No adverse effects were observed for any of the mentioned compounds of invention in the above test.

Compound	**Dose (mg / kg)**	**Reduction in Blood Glucose Level (%)**	**Triglyceride Lowering (%)**
Example 44	3 mg	52	31
Example 15	3 mg	72	69
Example 18	3 mg	49	40
Example 48	3 mg	52	19

The ob/ob mice were obtained at 5 weeks of age from Bomholtgard, Denmark and were used at 8 weeks of age. Zucker fa/fa fatty rats were obtained from IffaCredo, France at 10 weeks of age and were used at 13 weeks of age. The animals were maintained under 12 hour light and dark cycle at 25 ± 1°C. Animals were given standard laboratory chow (NIN, Hyderabad, India) and water, *ad libitum* (Fujiwara, T., Yoshioka, S., Yoshioka, T., Ushiyama, I and Horikoshi, H. Characterization of new oral antidiabetic agent CS-045. Studies in KK and ob/ob mice and Zucker fatty rats. Diabetes. 1988. 37: 1549–1558).

The test compounds were administered at 0.1 to 30 mg/kg/day dose for 9 days. The control animals received the vehicle (0.25 % carboxymethylcellulose, dose 10 ml/kg) through oral gavage.

The blood samples were collected in fed state 1 hour after drug administration on 0 and 9 day of treatment. The blood was collected from the retro-orbital sinus through heparinised capillary in EDTA containing tubes. After centrifugation, plasma sample was separated for triglyceride, glucose, free fatty acid, total cholesterol and insulin estimations. Measurement of plasma triglyceride, glucose, total cholesterol were done using commercial kits (Dr. Reddy's Laboratory, Diagnostic Division kits,

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Hyderabad, India). The plasma free fatty acid was measured using a commercial kit form Boehringer Mannheim, Germany. The plasma insulin was measured using a RIA kit (BARC, India). The reduction of various parameters examined are calculated according to the formula.

In ob/ob mice oral glucose tolerance test was performed after 9 days treatment. Mice were fasted for 5 hrs and challenged with 3 gm/kg of glucose orally. The blood samples were collected at 0, 15, 30, 60 and 120 min for estimation of plasma glucose levels.

The experimental results from the db/db mice, ob/ob mice, Zucker fa/fa rats suggest that the novel compounds of the present invention also possess therapeutic utility as a prophylactic or regular treatment for diabetes, obesity, cardiovascular disorders such as hypertension, hyperlipidaemia and other diseases; as it is known from the literature that such diseases are interrelated to each other.

Blood glucose level and triglycerides are also lowered at doses greater than 10 mg/kg. Normally, the quantum of reduction is dose dependent and plateaus at certain dose.

b) **Cholesterol lowering activity in hypercholesterolemic rat models**

Male Sprague Dawley rats (NIN stock) were bred in DRF animal house. Animals were maintained under 12 hour light and dark cycle at 25 ± 1°C. Rats of 180 - 200 gram body weight range were used for the experiment. Animals were made hypercholesterolemic by feeding 2% cholesterol and 1% sodium cholate mixed with standard laboratory chow [National Institute of Nutrition (NIN), Hyderabad, India] for 6 days. Throughout the experimental period the animals were maintained on the same diet (Petit, D., Bonnefis, M. T., Rey, C and Infante, R. Effects of ciprofibrate on liver lipids and lipoprotein synthesis in normo- and hyperlipidemic rats. Atherosclerosis. 1988. 74: 215–225).

The test compounds were administered orally at a dose 0.1 to 30 mg/kg/day for 3 days. Control group was treated with vehicle alone (0.25 % Carboxy-ethylcellulose; dose 10 ml/kg).

The blood samples were collected in fed state 1 hour after drug administration on 0 and 3 day of compound treatment. The blood was collected from the retro-orbital sinus through heparinised capillary in EDTA containing tubes. After centrifugation, plasma sample was separated for total cholesterol, HDL and triglyceride estimations. Measurement of plasma triglyceride, total cholesterol and HDL were done using commercial kits (Dr. Reddy's Laboratory, Diagnostic Division, India). LDL and VLDL cholesterol were calculated from the data obtained for total cholesterol, HDL and triglyceride. The reduction of various parameters examined are calculated according to the formula.

Compound	Dose mg/kg	Triglyceride (%)↓	Total Cholesterol (%)↓	HDL↑ (%)	LDL (%)↓	VLDL(%)↓
Example 6	3 mg	45	11	NE	11	25
Example 15	10 mg	38	20	4	21	33

↓ = reduction; ↑= increase; NE = no effect

c) <u>Plasma triglyceride and total cholesterol lowering activity in Swiss albino mice and Guinea pigs</u>

Male Swiss albino mice (SAM) and male Guinea pigs were obtained from NIN and housed in DRF animal house. All these animals were maintained under 12 hour light and dark cycle at 25 ± 1°C. Animals were given standard laboratory chow (NIN, Hyderabad, India) and water, *ad libitum*. SAM of 20 - 25 g body weight range and Guinea pigs of 500 - 700 g body weight range were used (Oliver, P., Plancke, M. O., Marzin, D., Clavey, V., Sauzieres, J and Fruchart, J. C. Effects of fenofibrate, gemfibrozil and nicotinic acid on plasma lipoprotein levels in normal and hyperlipidemic mice. Atherosclerosis. 1988. 70: 107–114).

The test compounds were administered orally to Swiss albino mice at 0.3 to 30 mg/kg/day dose for 6 days. Control mice were treated with vehicle (0.25% Carboxy-methylcellulose; dose 10 ml/kg). The test compounds were administered orally to Guinea pigs at 0.3 to 30 mg/kg/day dose for 6 days. Control animals were treated with vehicle (0.25% Carboxymethylcellulose; dose 5 ml/kg).

The blood samples were collected in fed state 1 hour after drug administration on 0 and 6 day of treatment. The blood was collected from the retro-orbital sinus through heparinised capillary in EDTA containing tubes. After centrifugation, plasma sample was separated for triglyceride and total cholesterol (Wieland, O. Methods of Enzymatic analysis. Bergermeyer, H. O., Ed., 1963. 211 - 214; Trinder, P. Ann. Clin. Biochem. 1969. 6 : 24 – 27). Measurement of plasma triglyceride, total cholesterol and HDL were done using commercial kits (Dr. Reddy's Diagnostic Division, Hyderabad, India).

Compound	Dose (mg / kg)	Triglyceride (%)↓
Example 42	3 mg	59
Example 35	1 mg	56
Example 28	10 mg	70
Example 40	10 mg	61
Example 64	10mg	57

Formulae for calculation:

1. Percent reduction in Blood sugar / triglycerides / total cholesterol were calculated according to the formula :

$$\text{Percent reduction (\%)} = \left[1 - \frac{TT / OT}{TC / OC}\right] \times 100$$

OC = Zero day control group value

OT = Zero day treated group value

TC = Test day control group value

TT = Test day treated group value

2. LDL and VLDL cholesterol levels were calculated according to the formula :

$$\text{LDL cholesterol in mg/dl} = [\text{Total cholesterol} - \text{HDL cholesterol} - \frac{\text{Triglyceride}}{5}] \text{ mg/dl}$$

VLDL cholesterol in mg/dl=[Total cholesterol-HDL cholesterol-LDL cholesterol] mg/dl